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January 1980

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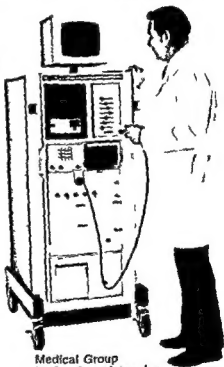
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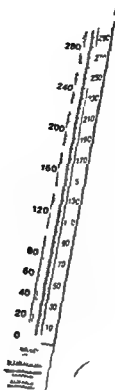
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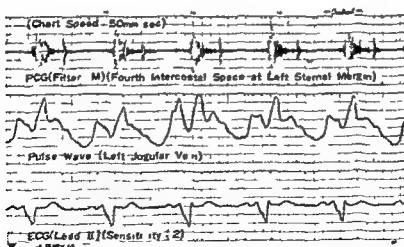
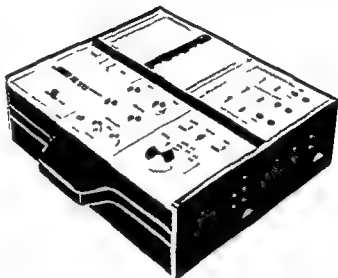
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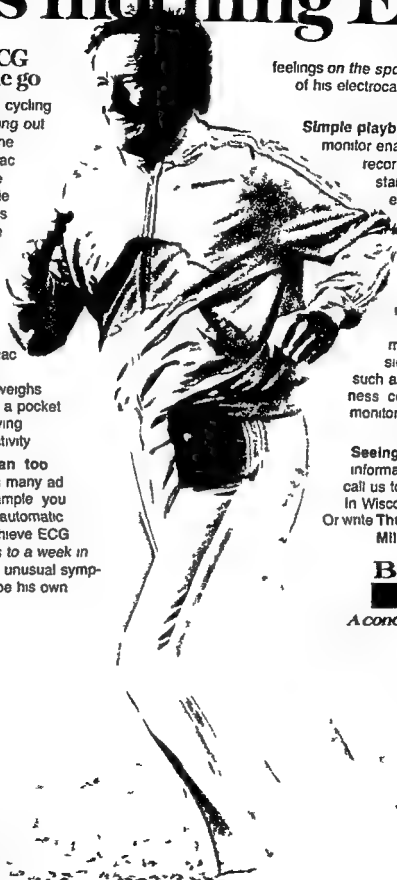
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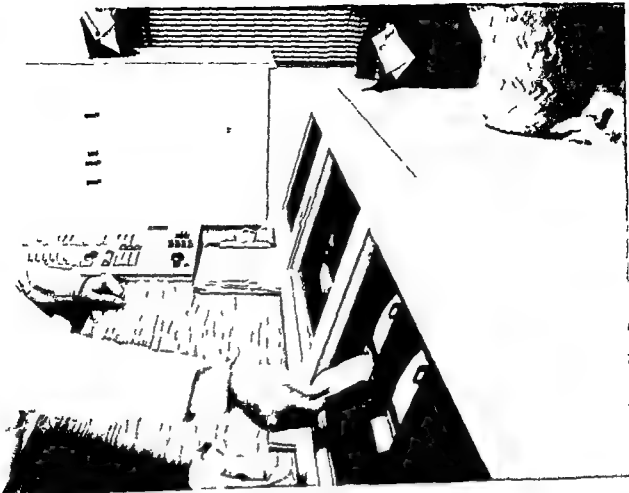


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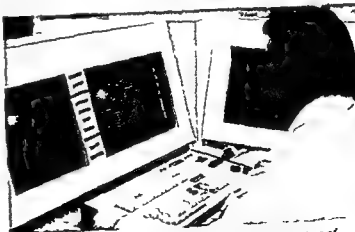
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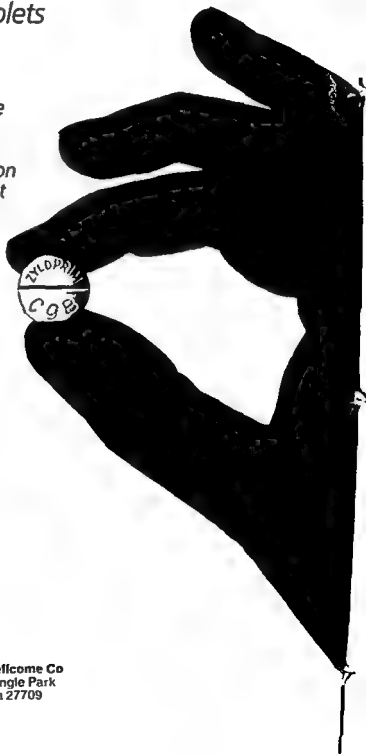
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## Editorial

### Brain peptides and pain sensation

W J Jeffcoate MA MRCP

London England

Auntie did you feel no pain  
Falling from that apple tree?  
Would you do it please again?  
Cos my friend here didn't see  
Harry Graham (1874-1936)

In certain circumstances extensive physical injuries can be sustained and yet give rise to no immediate pain. The explanation remained obscure until very recently when the discovery of the enkephalins and the endorphins led to exciting speculation concerning the role of endogenous morphine like substances.<sup>1</sup> Thus it seems that a number of these opioid peptides occur in the brain, cerebrospinal fluid, pituitary, and plasma and that they are released by stress and other stimuli to induce analgesia. It has been suggested also that their release mediates the analgesia induced by acupuncture and that alteration in levels of endogenous opioid peptides may underlie certain psychiatric diseases. While such theories are undoubtedly fascinating they are by no means proven.

#### Endogenous opioid peptides

The first substances with morphine like properties to be isolated from brain were two closely related pentapeptides, methionine and leucine enkephalin. The observation that methionine

enkephalin represented a small fragment of the 9 amino acid pituitary hormone  $\beta$  lipotropin ( $\beta$  LPH) led to other fragments of the hormone being studied. Four such fragments ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  endorphin) were found to have morphine like activity,  $\beta$  endorphin being the most potent.

The parent molecule  $\beta$  LPH was first isolated in 1964 by Dr C H Li and colleagues, but after early theories concerning a possible role in the control of fat metabolism had been discarded it remained a peptide of no known function. However, it is thought to be formed by enzymatic cleavage from the same precursor molecule as adrenocorticotropin (ACTH) and large molecular weight precursors have been identified.  $\beta$  LPH and ACTH are found in the same cells of the pituitary gland and the two are released together both basally and in times of stress. Therefore the discovery that fragments of  $\beta$  LPH possessed morphine like activity (even though  $\beta$  LPH itself does not) seemed to make teleological sense: endogenous opioid peptides were derived from a pituitary stress hormone and would be available at times when painful injuries are likely to be sustained.

#### Measurement of endogenous opioid peptides

The enkephalins and endorphins, unlike  $\beta$  LPH, share the ability to bind to opiate receptors in animal tissue such as those on rat brain synaptosomes, mouse vas deferens, and guinea pig ileum. As this binding is stereospecific and competitively reversed by the morphine antagonist naloxone, it has been used as the basis of

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number of *in vitro* bioassays'. Unfortunately these assays do not differentiate between individual opioid peptides. Specific radioimmunoassays for methionine and leucine enkephalins are now becoming available<sup>1</sup>, but it has not yet been possible to identify enkephalins circulating in either animal or human plasma.

The measurement of the endorphins by specific radioimmunoassay poses special problems. For theoretical reasons antisera developed to  $\beta$ -endorphin will almost always cross-react with the enkephalins, the other endorphins or with the parent molecule  $\beta$ -LPH. This lack of specificity means that extreme care is necessary for the interpretation of levels of apparent  $\beta$ -endorphin immunoreactivity in various animal fluids. At the moment it is necessary to incorporate at least one chromatographic stage for the positive identification of any of the endorphins: less exacting data merely provide suggestive evidence.

#### Are opioid peptides concerned with endogenous analgesia?

There is a mass of highly suggestive circumstantial evidence to implicate the involvement of an opioid pathway in endogenous analgesic mechanisms, although most of this evidence is derived from study of morphine antagonists. Thus naloxone has been shown to lower the resting pain threshold in both mice and men, and to reverse the analgesic effect of hypnosis and placebo. Moreover the profound analgesia which is induced by electrical stimulation of the periaqueductal grey matter is also partially reversed by the administration of a morphine antagonist. In addition Akil and colleagues have recently shown that in humans analgesia achieved by stimulation of the periaqueductal grey matter is associated with a rise in enkephalin-like material in cerebrospinal fluid.

Further support comes from immunofluorescent studies which have been performed to localize the enkephalins and endorphins in different tissues. Although the peptides are found in most parts of the central nervous system as well as in the anterior and intermediate lobes of the pituitary gland they are present in particularly high concentration in those areas thought to be associated with modification of pain sensation: the substantia gelatinosa of the dorsal horns in the spinal cord and the periaqueductal grey matter of the brain stem.

#### Unsolved problems

It seems likely that with the development of more sensitive and specific techniques for the assay of the enkephalins and the endorphins these peptides will be shown to play a major role in the modification of pain sensation. Moreover such techniques will help solve some of the problems that have been encountered.

**A Relationship between  $\beta$ -LPH and opioid peptides in pituitary and brain.** Data currently available have failed to establish any relationship between the levels of apparent endorphin or enkephalin in CSF, brain and plasma. Patients with hypopituitarism have normal levels of immunoreactive  $\beta$ -endorphin in CSF, and hypophysectomy has no effect on the brain content of opioid peptides in experimental animals. If it is true that opioid peptides present in brain are not derived from the pituitary, the significance of  $\beta$ -LPH being a stress hormone is lost and indeed  $\beta$ -LPH becomes once more a pituitary peptide of unknown function. Moreover  $\beta$ -LPH is related structurally only to methionine-enkephalin and there is no equivalent parent molecule for leucine enkephalin.

**B Why are there so many opioid peptides?** As all of the enkephalins and endorphins have qualitatively similar actions, there is no apparent reason for their separate existence. While it may be that  $\beta$ -endorphin is the major opioid peptide and that the other endorphins together with methionine enkephalin merely represent different stages of its metabolism, it seems more likely that a discrete role will be found for each of these substances. In particular the distribution of the enkephalins in nerve terminals<sup>1</sup> and the existence of pathways for their rapid breakdown suggest that they act as neurotransmitters. On the other hand the endorphins are comparatively stable in body fluids and they may well act as neuromodulators rather than transmitters.

Whatever the physiological action of these substances is finally shown to be, their discovery has reawakened interest in the study of opiate drugs. It is to be hoped that such work will lead to greater understanding of the way in which these drugs act and eventually will lead to the development of more effective means of controlling pain.

I thank Professor Lesley Rees and Professor Michael Besser for their advice and support.

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## Clinical setting and prognostic significance of high degree atrioventricular block in acute inferior myocardial infarction a study of 144 patients

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Atrioventricular (AV) block has been reported in 12 to 25% of patients with acute myocardial infarction.<sup>1-3</sup> All forms of AV block occur two to four times more frequently in acute inferior myocardial infarction (IMI) as compared to anterior myocardial infarction. The conduction disturbances during acute IMI are usually located in the AV node,<sup>4,5</sup> presumably due to a lesion proximal to the origin of the AV nodal artery; the latter is in 90% of cases a branch of the right coronary artery.<sup>6</sup>

It has been proposed that indications for pacemaker therapy in AV block complicating acute IMI are Stokes Adams attacks, power failure (congestive heart failure or shock) and bradycardia dependent ventricular arrhythmias. However, in the subgroup with power failure it is unclear and controversial as to whether pacemaker therapy influences immediate prognosis.<sup>7</sup>

This study therefore evaluates the clinical setting and prognostic significance of high degree AV block in acute IMI as well as the therapeutic value of pacing. From these data we will try to outline more precisely indications for pacemaker therapy.

### Material and methods

The subjects were patients admitted to the coronary care unit because of acute IMI.

The diagnosis of acute infarction was based on a typical history of chest pain correlated with the appearance of diagnostic Q waves and characteristic serial changes in serum enzymes. In all patients continuous electrocardiographic monitoring was performed. The location of infarction was defined according to the criteria of the New York Heart Association.<sup>8</sup> IMI included diaphragmatic and/or posterior infarction with or without lateral involvement. Patients with both anterior or anteroseptal and inferior infarction were excluded from the study. High degree AV block was defined as the presence of second degree AV block occurring via a type I mechanism, two to one block, atrial fibrillation with a ventricular rate of less than 60/minute provided that the patient did not use digitalis, and third degree AV block.

In third degree AV block the atrial rate was always considerably higher than the ventricular rate.

Only those patients were included in the study in whom the AV block lasted for at least half an hour. The presence and degree of power failure at the time of onset during and following the episode of high degree AV block were noted. Severe power failure was defined as shock (a systolic blood pressure of less than 90 mm Hg, peripheral vascular constriction and an altered sensorium). Shock was considered irreversible

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**Table I** Incidence age sex mean peak SGOT and mortality rate

	All pts with IMI	Pts without high degree AV block	Pts with high degree AV block
No	843	699	144
Mean age (yr)	63	62	65
Sex			
male	624	517	110
female	216	182	34
Mean peak SGOT (IU)	100	92	140
Mortality rate (%)	12	9	22

when it persisted despite appropriate therapy including pacing.

The significance of differences between mean ages and mean peak values for SGOT were tested with Student's *t* test. A chi square test was used to test the significance of differences in incidence.

## Results

**Incidence and mortality rate** In a period of 5 years (1972 to 1976) 843 patients were admitted to the coronary care unit because of acute IMI. Of these 144 (17%) had high degree AV block (Table I). The mean age of the patients with high degree AV block was higher (65 years) than that (62 years) of those without high degree AV block ( $p < 0.01$ ). The mean peak SGOT was significantly higher ( $p < 0.001$ ) in the patients with high degree AV block (140 IU) than in those without AV block (92 IU). The hospital mortality rate of patients with acute IMI complicated by high degree AV block was significantly higher of the 144 patients 32 died (22%) compared to 65 (9%) of the 699 patients without high degree AV block ( $p < 0.001$ ). This difference was even significant if both subgroups were matched for age.

The cause of death in the patients with AV block was primarily power failure of the 32 patients 18 died of cardiogenic shock and six of congestive heart failure. Five patients died of cardiac rupture. In two patients the cause was non cardiac and in one it was unknown.

**Electrocardiographic course of high degree AV block** The maximal degree of AV block did not influence the immediate prognosis 12 of 50

**Table II** ECG prior to and following second degree AV block

	No	Totals
1 → 2	59	
Normal PR →	7	
On admission	25	
		91 { → 3 41 → 1 11 → † 7

1 = first-degree AV block 2 = second-degree AV block 3 = third-degree AV block

† = death during second-degree AV block

PR = PR interval.

**Table III** ECG prior to and following third degree AV block

	No	Totals
1 → 2 →	24	
2 →	17	
Normal PR →	9	
On admission	44	
		94 { → 2 → 1 60 → 1 24 → † 10

1 = first-degree AV block 2 = second-degree AV block 3 = third-degree AV block

† = death during third-degree AV block.

PR = PR interval.

patients (24%) with second degree AV block only died compared to 20 of 94 (21%) with third-degree AV block. Second-degree AV block was registered in 91 patients (Table II). In 59 of these first degree AV block was noticed prior to the onset of second degree AV block while in the 32 others it was the first manifestation of the AV conduction disturbance in the coronary care unit. In 41 patients (45%) the conduction disturbance progressed into third degree AV block. Seven patients died during second degree AV block and five others died after returning to 1:1 AV conduction.

Ninety four patients demonstrated third degree AV block (Table III). As mentioned 41 patients progressed from first and/or second degree to third-degree AV block while 53 patients manifested it as their initial conduction disturbance. Eighty four patients returned to 1:1 AV conduction either through a phase of second degree AV block (60) or directly (24). Ten patients died during third degree AV block while ten others died after returning to 1:1 AV conduction. All survivors of high degree AV block were discharged from the hospital with 1:1 AV conduction.

Table IV Escape frequency during third degree AV block

Beats/min.	No	Mortality (%)	PM (%)
≤ 30	8	4	0
31-40	34	6	26
41-50	32	4	2
51-60	1	0	9
61-70	3	1	1
> 70	2	0	1

PM = temporary pacemaker therapy

Table V Management of high degree AV block

	No	Mortality	
		No	%
PM	83	18	21
None or Atropine	61	14	23
Total	144	32	22

PM = temporary pacemaker therapy

**Time of onset of high degree AV block** In almost half of the patients (69 of 144) the high degree AV block was already present on admission. In only five of these 69 was the delay between onset of symptoms of IMI and admission longer than 24 hours. Of the 44 patients with third-degree AV block on admission 27 had a Stokes Adams attack and/or syncope prior to admission. High degree AV block had developed within 24 hours after onset of symptoms in 69% and within 3 days in 92% of the patients. The latest observed onset of high degree AV block was on the fifth day of IMI. The duration of high degree AV block varied from half an hour to 16 days. It was less than 24 hours in 37% and more than 11 days in 47% of the patients.

**Width of the QRS complexes during third degree AV block** An escape rhythm with widened (more than 0.12 sec) QRS complexes was observed in 35 of the 94 patients (37%). They all had narrow QRS complexes in the conducted beats. These widened QRS complexes had a left bundle branch block configuration in seven patients, a right bundle branch block configuration in 21 and both LBBB and RBBB in seven patients. The mechanisms of these widened QRS complexes have been described before.<sup>1</sup>

**Escape frequency during third-degree AV**

**block** Mortality was not influenced by the rate of the escape pacemaker at the time of onset of AV block being 19% (14 of 74) when the rate was ≤ 50/minute and 30% (six of 20) when it was > 50/minute (NS). Sixty of the 74 patients (81%) with a frequency ≤ 50/minute were treated with a temporary pacemaker compared to 11 of the 20 patients (55%) with a frequency > 50/minute (Table IV).

**Management** Eighty five of the 144 patients with high degree AV block (59%) were temporarily paced (Table V) according to the indications listed before. Of the 59 patients not paced eight were successfully treated with atropine whereas in the other 51 patients no treatment was necessary. The mortality rate of the patients who were paced (21%) was not significantly different from that of the patients who were not paced (24%).

#### Hemodynamic condition and ventricular rate

Forty two of the 144 patients demonstrated shock either at the time of onset of the AV block or when the high degree AV block was already present on admission (Table VI). Thirty one of these 42 patients had a ventricular rate of 50 per minute or less. Eleven of these 31 patients were initially treated with atropine with only one improving. One patient improved without treatment. Twenty nine of these 31 patients were treated with a temporary pacemaker and the shock was found to be reversible in 24 with only one late death. The remaining five patients did not respond to pacemaker therapy and died in irreversible shock.

Eleven of the 42 patients in shock had a ventricular rate of more than 50 per minute and six were paced. Three of these six showed initial improvement of their hemodynamic condition with only one late death. The other three did not respond to pacemaker therapy and died in irreversible shock. The remaining five patients were not paced because four had second-degree AV block only with a ventricular rate of 80 per minute or more and one refused pacemaker insertion. All five died in irreversible shock. Of the 102 patients who were not in shock at the time of onset of high degree AV block 17 died.

A Stokes Adams attack and/or syncope prior to admission occurred in 22 of the 31 patients (71%) with initial shock and a ventricular rate of less than 50 beats per minute in three of the 11 patients (27%) with shock and a ventricular rate

Table VI Hemodynamic condition and ventricular rate during high degree AV block

Management	Shock						No shock		
	VR $\leq 50/\text{min}$			VR $> 50/\text{min}$					
	No	Mortality		No	Mortality		No	Mortality	
		No	%		No	%		No	%
PM	29	6	21	6	4	67	50	11	16
None or Atropine	2	0	0	5	5	100	52	9	17
Total	31	6	19	11	9	82	102	17	17

VR = ventricular rate PM = temporary pacemaker therapy

$p < 0.005$

of more than 50 beats per minute and in 19 of the 102 patients (19%) who were not in shock

### Discussion

Patients with acute inferior myocardial infarction complicated by high degree AV block have a higher mortality rate than do those without high degree AV block (Table I). Also there is a high incidence of severe power failure especially at the time of the first manifestation of the high degree AV block in the coronary care unit. There are two possible explanations for these findings. Either the high degree AV block may only be a manifestation of an inferior infarction with more extensive myocardial damage as manifested by a higher mean peak SGOT or the conduction disturbance itself may contribute to the development of power failure, extension of infarction and hence a higher mortality.

In contrast to Rotman and associates<sup>3</sup> our data indicate that even patients with high degree AV block and no severe power failure had a higher mortality rate (17%) than did patients with IMI without high degree AV block (9%  $p < 0.05$ ). In the subgroup with high degree AV block without severe power failure there was no difference in mortality rate between those who were paced (16%) and those who had an acceptable ventricular rate and did not need a temporary pacemaker (17%) (Table VI). We believe that in this group of patients without severe power failure the higher mortality rate is mainly due to more extensive myocardial damage and not to the AV block itself. However there seems to be a subset of patients with high degree AV block in which the conduction disturbance contributes to the subsequent clinical course.

The characteristics of these patients are severe power failure at the time of onset of the high degree AV block associated with a low ventricular rate.

It appeared that in this group of patients with shock the ventricular rate was of prognostic significance (Table VI). 31 patients were in shock and had a ventricular rate of 50 per minute or less. Most of these patients were paced and it was found that in the majority the shock was reversible soon after pacing was started. The mortality rate in this group with initial shock and a low ventricular rate was 19% which is not significantly different from the mortality rate (17%) of the group without severe power failure. However when the ventricular rate was more than 50 per minute most of the patients with shock did not respond to treatment and died in irreversible shock. In these patients pacemaker therapy seems not to affect the immediate prognosis. We believe that in patients presenting with both high degree AV block and shock it is not possible to distinguish between irreversible shock secondary to massive myocardial damage and reversible shock caused by both extensive myocardial damage and the conduction disturbance itself. The latter situation seems to occur especially in patients with shock and a low ventricular rate. We are aware that we as well as others<sup>3,11</sup> do not have hard data to establish this statement but it is in our view unethical to determine the true natural history of symptomatic high degree AV block complicating acute IMI by withholding pacemaker therapy in such patients.

A possible reason for the high incidence of reversible shock that cannot be ruled out in our patients is right ventricular infarction. Right

ventricular involvement in IMI is reported to occur in 40% of cases<sup>1</sup> with hemodynamic alterations such as a lowered right ventricular ejection fraction.<sup>11</sup> Recently Lorell and colleagues reported that temporary pacing did not alleviate hypotension in patients with IMI and a right ventricular infarction. From 12 patients with IMI right ventricular infarction and arterial hypotension nine needed temporary pacing but in none was hypotension corrected by pacing alone. In contrast our patients with reversible shock did show improvement of the hemodynamic condition soon after pacing (the only therapy) was started.

Therefore we believe that more data are necessary to evaluate the effect of cardiac pacing on both right and left ventricular function in patients with high degree AV block complicating acute IMI who are either symptomatic or have a low ventricular rate.

### Summary

High degree AV block occurred in 144 of 843 patients consecutively admitted because of acute inferior myocardial infarction and was associated with more extensive myocardial damage and a higher mortality rate as compared to those without AV block.

Patients with power failure at the time of appearance of high degree AV block and a ventricular rate of less than 50 per minute seemed to profit from pacemaker therapy.

By contrast in patients with power failure and a ventricular rate of more than 50 per minute pacemaker insertion did not affect immediate prognosis.

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## The heart in chronic alcoholism: a noninvasive study

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An association between chronic alcoholism and cardiac dysfunction has been studied and documented repeatedly. Moreover, some alcoholic subjects develop severe congestive heart failure presumably secondary to alcoholic cardiomyopathy.<sup>1-3</sup>

It has been reported that acute administration of alcohol may also produce transient abnormality of cardiac function.<sup>4</sup> Chronic alcoholic individuals without clinical evidence of heart disease may have abnormal systolic time intervals.<sup>5,6</sup> The hearts of chronic alcoholic patients dying of non-cardiac causes show ventricular hypertrophy at autopsy.

In the present investigation, a noninvasive evaluation of the hearts of chronic alcoholic subjects without clinical evidence of heart disease was performed by combining an echocardiographic examination with the determination of systolic time intervals.

The objective was to ascertain whether structural or functional cardiac abnormalities exist in alcoholic subjects without apparent evidence of heart disease.

### Material

Eighty-five male chronic alcoholic subjects below the age of 45 years were studied. In 73 of them, high quality echocardiographic tracings

were obtained and are the subject of this study (Group A = alcoholics).

The patients were admitted to the alcohol detoxification unit of the Hospital for Joint Diseases & Medical Center during the period of 1976 to 1978 and were studied between 3 and 6 days after admission. All had been drinking an amount equivalent to at least 12 oz of whiskey daily for at least five years. None had any history of heart or lung disease, hypertension, or diabetes. Physical examination in all revealed normal blood pressure and no evidence of congestive heart failure. Since sex difference has been reported in the effect of alcohol on the heart, only males were examined.<sup>7</sup> To decrease the probability of concomitant coronary artery diseases, only patients below the age of 45 years were investigated.

As a control group, 30 carefully selected male hospital employees without any clinical evidence of or history of heart disease were studied (Group N = normal controls). All were below the age of 45 years. None had high blood pressure and none drank more than small amounts of alcohol occasionally. As a comparison group, nine male alcoholic subjects with severe congestive heart failure were studied (Group C = alcoholics with congestive heart failure). All were also below the age of 45 years, all were studied at the same time period, and none presented either history or evidence suggesting valvular, coronary, or hypertensive cardiovascular disease. They were presumably patients with alcoholic cardiomyopathy. In two of those patients, cardiac catheterization confirmed the diagnosis of congestive cardiomyopathy.

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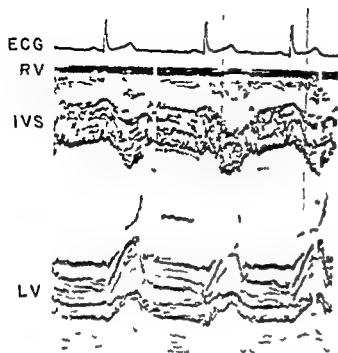


Fig 1 Echocardiogram of a chronic alcoholic patient revealing increased thickness of the interventricular septum (IVS) = 14 mm, and posterior wall of the left ventricle (LV) = 12 mm. The myocardial contractility is normal. ECG = electrocardiogram RV = right ventricle

## Methods

Systolic time intervals were calculated from Lead II of the electrocardiogram and the phonocardiogram recorded at the left sternal border and carotid pulse tracing. The tracings were recorded utilizing a VR 6 Electronics for Medicine recorder at a paper speed of 100 mm/sec. Five complexes were measured and averaged (all patients were in sinus rhythm). The rate correction of left ventricular ejection time (LVET) was calculated according to the method of Weissler and associates.<sup>10</sup>

Left ventricular ejection time (LVET) was measured from the upstroke of carotid pulse to the incisura. Pre ejection period (PEP) was calculated as the difference between the Q-A<sub>1</sub> interval and LVET. The Q-A<sub>1</sub> interval was measured from the beginning of the QRS complex to the first component of the second heart sound.

Echocardiograms were obtained with a VR6 Electronics for Medicine recorder with an 8.5 inch 2.25 MHz transducer focused at 5 cm. Echocardiograms were recorded with subjects in a slightly left lateral decubitus position. After

obtaining clear mitral echoes of both anterior and posterior leaflets the transducer was angled laterally and inferiorly to obtain clear septal and posterior wall endocardial echoes (Fig 1). The ventricular dimensions were measured at the level of the chordae tendineae. All diastolic echocardiographic measurements were made at the beginning of the QRS complex according to the Committee on M Mode Standardization of the American Society of Echocardiography.

The following formulae were used:  
Shortening Fraction (SF%)

$$\frac{Dd - Ds}{Dd} \times 100 \text{ where} \quad (1)$$

Dd = diastolic dimension Ds = systolic dimension

Ejection Fraction (EF)

$$\frac{EDV - ESV}{EDV} \text{ where} \quad (2)$$

EdV = end diastolic volume ESV = end systolic volume and SV = stroke volume

Cardiac volumes were calculated according to the Teicholtz correction<sup>11</sup>

$$V = D^3 \times \frac{70}{D + 24} \text{ where} \quad (3)$$

V = volume D = dimension

Mean velocity of circumferential fiber shortening (VCF<sub>cc</sub> / s)<sup>12</sup>

$$\frac{Dd - Ds}{Dd \times LVET} \text{ where} \quad (4)$$

LVET = left ventricular ejection time

Left ventricular mass (LV mass gm) was obtained by a modification of the method of Troy and colleagues.<sup>13</sup>

$$105 [(Dd + IVS + LV_1) Dd^2] \text{ where} \quad (5)$$

IVS, = interventricular septum thickness and LV<sub>1</sub> = left ventricular wall thickness

Normalized left ventricular posterior wall Velocity (VpW cm / sec)<sup>14</sup>

Table 1 General evaluation and systolic time interval in three groups\*

Groups†	No	Age (yr)	BSA (M <sup>2</sup> )	Blood pressure (mm Hg)		HR (min)	Year of drinking	PEP (Sec)	LVET (Sec)	LVETI (Sec)	PEP/ LVET	C/T	SV + RV (mm)
				Syst	Diast								
A	73	34.4	1.77	117	77	76	15.2	0.106	0.290	0.400	0.295	0.45	32
±SD		6.0	0.17	9.8	9.3	12	7.0	0.012	0.030	0.028	0.036	0.043	8.9
N	30	32.4	1.84	117	76	76	—	0.097	0.297	0.416	0.313	0.44	30.5
±SD		5.7	0.23	10.0	—	—	—	0.014	0.029	0.074	0.061	0.037	9.4
C	9	36.1	1.83	117.6	78	98.3	19.1	0.131	0.206	0.372	0.600	0.61	29.4
±SD		6.2	0.13	11.8	6	12.8	5.0	0.017	0.029	0.021	0.116	0.04	11.5
p value													
A vs N		NS	NS	NS	NS	NS	—	<0.001	<0.001	<0.01	<0.001	NS	NS
N vs C		NS	NS	NS	NS	<0.01	—	<0.001	<0.001	<0.001	<0.001	<0.001	NS
A vs C		NS	NS	NS	NS	<0.01	NS	<0.001	<0.001	<0.01	<0.001	<0.001	NS

\*Mean and standard deviation.

†A = alcoholics; N = normal controls; C = alcoholics with congestive heart failure. BSA = body surface area; HR = heart rate; PEP = pre-ejection period; LVET = left ventricular ejection time; LVETI = left ventricular ejection time index; C/T = cardiac thoracic ratio; SV + RV = the sum of the amplitude of the S wave in Lead V and R wave in Lead V.

$$\frac{PWE}{LVET \times Dd} \quad \text{where} \quad (6)$$

PWE = posterior wall excursion  
Normalized interventricular septal velocity  
(Vivs cm/sec)

$$\frac{IVSE}{LVET \times Dd} \quad \text{where} \quad (7)$$

IVSE = interventricular septal excursion

All echocardiographic measurements were corrected for body surface area (BSA)

A detailed medical history, physical examination, 12 lead electrocardiogram and posteroanterior chest x ray were performed

The mean and standard deviation values were calculated and the data were subjected to Student's t test

## Results

The non cardiac alcoholic subjects (Group A) did not differ from normal controls (Group N) in age, body surface area, heart rate, blood pressure and cardiothoracic ratio (Table I)

**Electrocardiogram** There was no difference

Since BSA correction did not significantly change any of the data instead of presenting two sets of data (corrected and uncorrected) the echocardiographic measurements are presented in the uncorrected form only and the left ventricular volumes and mass are presented in the unitary BSA corrected form.

either in the voltage of QRS complexes or the incidence of ST-T abnormalities between the normal subjects and non cardiac alcoholic subjects

The electrocardiograms of alcoholic patients with cardiomyopathy (Group C) were abnormal in all cases. All patients had evidence of left atrial enlargement (except one patient with atrial fibrillation). Marked ST-T abnormalities were present in all of them and left ventricular hypertrophy was present in seven out of nine.

**Systolic time intervals** Both groups of alcoholic subjects, cardiac and non cardiac, had abnormal systolic time intervals. Pre-ejection period was prolonged. Left ventricular ejection time was shortened and therefore PEP/LVET increased (Table I). These abnormalities were most marked in patients with congestive heart failure.

**Echocardiograms** The echocardiograms of non cardiac alcoholic subjects (Group A) when compared with normal controls revealed highly significant thickening of the interventricular septum and the left ventricular wall as well as the increase of the left ventricular mass ( $p < 0.001$ ) (Table II).

Fifty two per cent of the patients in Group A (Fig. 1) had markedly increased left ventricular mass (2 SD above the mean of the normal controls (Table III). Left ventricular thickness and interventricular septal thickness were

Table II Echocardiographic data in three groups\*

Group†	No	Dd (mm)	Ds (mm)	LA (mm)	IVSt (mm)	LVI (mm)	PWF (mm)	IVSL (mm)	SF (°)
A	73	49.5	31.1	29	11.71	10.4	11.5	8.1	37
±SD		11	4.9	4.8	1.33	1.0	2.2	2.7	6.5
N	30	47	30.4	28.3	9.63	8.76	11.7	7.7	35
±SD		4.3	4	4.3	1.94	0.86	2.3	2.1	4.5
C	9	66.9	39	43	11.78	11.28	6.4	2.9	11.8
±SD		5.9	7.2	6.7	1.6	1.39	2.7	1.0	3.0
p value									
A vs N		<0.001	NS	NS	<0.001	<0.001	NS	NS	NS
N vs C		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
A vs C		<0.001	<0.001	<0.001	NS	<0.001	<0.001	<0.001	<0.001

Mean and standard deviation

Abbreviation as in Table I. Dd = diastolic dimension. Ds = systolic dimension. LA = left atrial dimension. IVSt = interventricular septal thickness. LVI = left ventricular thickness. PWF = posterior wall excursion. SF = shortening fraction. VCF = velocity of mean circumferential fiber shortening. IVSV = left ventricular systolic volume. SV = stroke volume. FF = ejection fraction. IV mass = left ventricular mass. VpW = normalized anterior wall velocity. VvW = normalized interventricular septal velocity. IVSV = interventricular septal excursion.

The addition of 1.1 (index) to all values means body surface correction.

Table III Incidence of abnormalities (above or below 2 SD from normal controls)

Group	PF†	LVFT†	IFI / VVT†	C/T	Dd	Ds	IVSt	LVI	LVDV†	LVS†	LV mass†
A	10(13.7)	6(8.2)	14(19.2)	6(8.3)	10(13.7)	6(8.3)	71(42.5)	34(46.6)	9(12.3)	15(20.5)	38(52)
N	0	0	0	1(3.3)	0	1(3.3)	0	0	1(3.3)	1(3.3)	1(3.3)

N = number of subject. Percentage in parentheses.

Abbreviation as in Table I and II.

increased 2 SD above mean of normal control in 47% and 43% respectively (Table III).

There was a slight increase in the systolic dimension of the left ventricular cavity and both end systolic and diastolic volumes (Figs 2 and 3). Even though these differences could be considered significant ( $p < 0.05$ ) they are nevertheless small and may still be within the error of manual measurement.

Three patients had asymmetric septal hypertrophy (septal to posterior wall thickness ratio more than 1.3). Two of these had systolic anterior motion of the mitral valve (Fig 4).

However in these patients the septal motion was normal unlike that seen in idiopathic hypertrophic subaortic stenosis.

In Group A the indices of contractility (shortening fraction, ejection fraction, circumferential fiber shortening and velocities of the septum and posterior wall) were all normal. In contrast the patients with cardiomyopathy had markedly dilated left ventricles, thickened septa and posterior walls and greatly depressed indices of contractility (Fig 5).

When non cardiac alcoholic subjects were divided according to the duration of drinking (Table IV) there were no significant differences either in echocardiographic parameters or in systolic time intervals between the group drinking for 5 to 14 years and that drinking for 15 to 30 years.

## Discussion

Cardiac dysfunction in asymptomatic alcoholic subjects had been known since Spodick and associates and later others<sup>1-4</sup> reported prolonged pre ejection period, shortened ejection time and increased PEP/LVET ratio. Our results are very similar.

The objective of this study was to find out whether corresponding abnormalities of cardiac function could be established by echocardiography. Marked increase of the thickness of the interventricular septum and the left ventricular wall were observed together with a small increase in the size of the left ventricular cavity and a corresponding marked increase of the left ventricular mass.

VCF (Circ/Sec)	LV DVI (ml/M <sup>2</sup> )	LV SVI (ml/M <sup>2</sup> )	SVI (ml/M <sup>2</sup> )	EF	LV mass I (gm/M <sup>2</sup> )	VpW (cm/sec)	Vvis (cm/sec)
1.39	65	22.5	43.3	0.66	145.7	0.89	0.64
0.29	16	8.2	10.6	0.08	32	0.22	0.25
1.19	57.8	18.9	40	0.67	101	0.83	0.56
0.15	13.2	5.5	12.6	0.07	20.7	0.15	0.16
0.59	124.1	31.1	31	0.25	242	0.39	0.21
0.21	18.6	15.6	10	0.07	53	0.16	0.08
NS	<0.05	<0.05	NS	NS	<0.001	NS	NS
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Chronic alcoholic subjects without cardiac symptoms were examined echocardiographically in two studies<sup>12, 14</sup> Those studies were published only in abstract form and the number of subjects was small Mathews and co-workers<sup>12</sup> studied 26 chronic non cardiac alcoholic subjects and found increased thickness of the septum and the left ventricle in 81% Our results are similar but the incidence of this abnormality was approximately 45% in our study This increased thickness is probably due to hypertrophy of the myocardium as is evident from pathological reports of Schenk and Cohen<sup>1</sup> However glycoprotein deposition demonstrated in a chronic animal experiment by Regan and colleagues<sup>13</sup> may be considered as potentially responsible for the increased thickness

In the absence of any other apparent causes it seems likely that cardiac hypertrophy in subjects studied was due to the influence of alcohol

Knowing that systolic time intervals are abnormal in chronic alcoholic subjects we expected to find an evidence of decreased myocardial contractility on echocardiogram However all echocardiographic indices of contractility appear to be normal and do not differ from a control group Fernando and Friedman<sup>1</sup> reported even hyperdynamic echocardiograms in alcoholic patients with cirrhosis of the liver

Having the benefit of recording both systolic time intervals and the echocardiogram we would like to explain why the indices of cardiac contractility are echocardiographically normal while systolic time intervals are abnormal It appears that either systolic intervals are more sensitive in evaluating myocardial contractility or that abnormal systolic time intervals are due to other causes than decreased contractility The former

alternative even though quite possible has not been investigated and latter seems to be likely

Regan and associates<sup>13</sup> postulated that abnormal systolic time intervals in alcoholic subjects are due to abnormal compliance of the left ventricle

The main finding of our study is the presence of myocardial hypertrophy in chronic alcoholic individuals myocardial hypertrophy being one of the most important causes of decreased compliance<sup>14</sup>

Furthermore abnormal systolic time intervals may be due not only to decreased contractility but also due to decreased compliance of the myocardium<sup>14</sup> Finding marked hypertrophy of the heart normal indices of contractility by echocardiogram and abnormal systolic time intervals lead us to concur with the Regan hypothesis of decreased myocardial compliance as the possible mechanism of abnormal myocardial function in chronic alcoholic persons

Our three cases of asymmetrical septal hypertrophy (two with anterior systolic motion of the mitral valve) are of interest and add to the ever growing list of conditions simulating hypertrophic cardiomyopathy There is however a difference between our cases and patients with hypertrophic cardiomyopathy The septal motion is normal or increased in our subjects but diminished in cases of hypertrophic cardiomyopathy

Surprisingly there was no increase in cardiac abnormalities paralleling longer periods of alcoholism When the two groups were compared the first drinking for 5 to 14 years and the second drinking for 15 to 30 years there were virtually no differences in systolic time intervals or in echocardiographic findings It may appear that whatever hypertrophy occurs in chronic alcoholic subjects

Table IV Comparison of noninvasive studies according to duration of drinking\*

	%	Age	Years of drink	IEP	LVFTI	PFP/ LVFT	C/T	Dd	Ds	IVS
Group I (5-14 years of drinking)	32	30.1	8.9	0.105	0.399	0.394	0.45	43.0	31.5	11.7
		4.4	3.1	0.014	0.027	0.056	0.047	4.7	3.8	1.5
Group II (15-30 years of drinking)	41	37.6	20.3	0.106	0.401	0.396	0.45	43.8	30.8	11.7
		5.0	4.8	0.011	0.031	0.056	0.041	5.9	5.5	1.2
p value		<0.001	<0.001	NS	NS	NS	NS	NS	NS	NS

\*Mean and standard deviation.

Abbreviations in Tables I and II

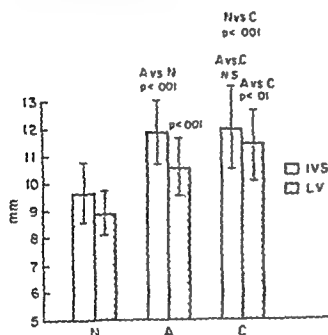


Fig 2 Thickness of the interventricular septum (IVS) = open bars and thickness of the posterior wall of the left ventricle (LV) = shaded bars, in three groups: N = normal controls, A = alcoholics, C = alcoholics with congestive heart failure. Vertical lines = standard deviation.

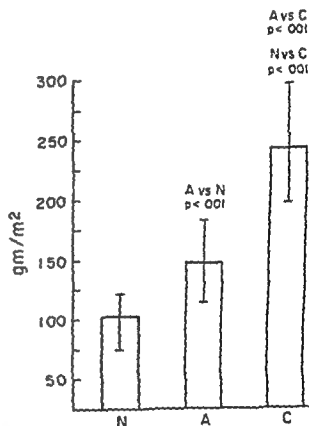


Fig 3 Left ventricular mass index (gm/M). Abbreviations as in Fig 2.

takes place in the first five years of the addiction. This conclusion, however, should be considered with caution because the information about duration of drinking cannot be considered very accurate since it depends to a large extent on the memory and interpretation of the subjects.

It is of interest that when former chronic alcoholic individuals abstained from drinking for a longer period, the echocardiogram showed no abnormalities. This may suggest a reversibility of earlier stages of cardiac involvement in chronic alcoholic subjects.

When comparing a group of non-cardiac alco-

holic subjects with those with alcoholic cardiomyopathy, it is apparent that a major difference is marked dilatation of the heart and decreased myocardial contractility in cardiomyopathy. Hypertrophy is present in both, however, but more severe in the cardiomyopathy group.

### Summary

The echocardiogram and systolic time interval were used to evaluate cardiac function in

LVt	ACF	SF	LV DI	LV SI	SVI	EF	LV mass l	IVW	IVS	SV + RV
106	132	307	616	279	417	064	145	087	063	344
12	019	39	141	66	95	003	276	016	019	94
103	144	381	604	271	445	067	145.8	090	066	314
09	034	77	172	92	112	009	350	025	020	84
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

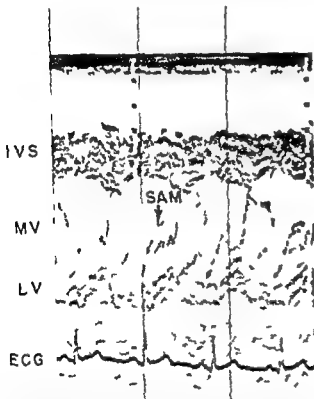


Fig 4 Echocardiogram of a chronic alcoholic subject. Systolic anterior motion of the mitral valve (SAM) marked with an arrow. Note septal hypertrophy. Abbreviations as in Fig 1

chronic alcoholic subjects without symptoms of heart disease. All were below the age of 45 years and none had arterial hypertension or history of heart disease. The echocardiograms of chronic alcoholic individuals revealed increased thickness of the left ventricular wall ( $10.4 \text{ mm} \pm 1.05$  normal controls  $8.76 \text{ mm} \pm .86$   $p < 0.001$ ) inter-ventricular septum ( $11.71 \text{ mm} \pm 1.33$  normal

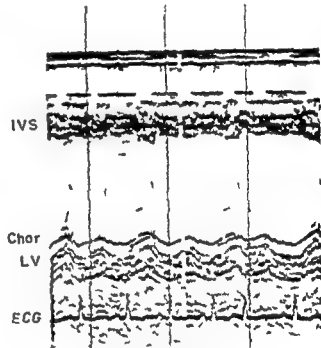


Fig 5 Alcoholic cardiomyopathy. Markedly dilated poorly contracting left ventricle. Abbreviations as in Fig 1

controls  $9.63 \pm 1.24$   $p < 0.001$ ) and markedly increased left ventricular mass ( $145 \text{ gm/M}^2 \pm 32$  normal controls  $101 \pm 20.7$   $p < 0.001$ )

The echocardiographic indices of myocardial contractility (ejection fraction, wall excursion and velocity circumferential fiber shortening) were normal. Systolic time intervals revealed shortening of ejection time and prolongation of the pre ejection period. It was found that approximately half of the asymptomatic alcoholic subjects have left ventricular hypertrophy without echocardiographic evidence of decreased myocardial contractility. It is suggested that

abnormal systolic time intervals may be due to decreased myocardial compliance

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## Truncus arteriosus malformation a spectrum including fourth and sixth aortic arch interruptions

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Truncus arteriosus malformation is a relatively rare form of congenital heart disease accounting for approximately 1% to 2% of autopsied patients with congenital heart defects.<sup>1</sup> The exact anatomic pattern of the great vessels varies and Van Praagh and Van Praagh<sup>2</sup> were the first to emphasize the inverse variation in development of the fourth and sixth aortic arches in this malformation. The impetus for persistence of both arches during fetal life is removed in truncus arteriosus malformation,<sup>3</sup> so that most cases show a well developed fourth arch with absence or only a ligamentous remnant of the ductus arteriosus; however, two recent series<sup>4,5</sup> report 14 to 23% of cases having a well developed sixth aortic arch associated with interruption of the ascending aorta. Collett and Edwards<sup>6</sup> noted only one such case.

Concepts of the pathogenesis of truncus arteriosus include primary deficiency of the conotruncal ridges<sup>1</sup> or primary failure of formation of the pulmonary conus. Other studies on normal cardiogenesis<sup>7</sup> and on truncus arteriosus malformation<sup>8</sup> have postulated a hemodynamic basis for the configuration of both the great

vessels and the semilunar valves. In the present study, all cases of truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital were reviewed and interpreted in relation to the three theories of pathogenesis. The results suggest that a hemodynamic explanation may account for the preferential development of either the fourth or the sixth aortic arch in truncus arteriosus malformation.

### Materials and methods

All patients with truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital for whom the heart was available for review were included in this study. Cases with either pulmonic or aortic atresia were omitted. Nineteen patients met the criteria for this study. The patients ranged in age from one day to 30 years old and included 12 males. Seven patients had no cardiac operations. In seven patients pulmonary artery banding only was performed. Three patients had right subclavian to pulmonary artery anastomoses and one had a descending aorta to left pulmonary artery anastomosis. One patient had total correction with right ventricle to pulmonary artery homograft ligation of the proximal pulmonary trunk and patching of the ventricular septal defect. Gross heart specimens were reviewed and a standard series of observations was made on each, including preferential aortic arch development (fourth vs sixth), origin of truncus from either left ventricle predominantly, right ventricle predominantly, or straddling the ventricular septum, state of inter-ventricular septum, number of semilunar valve cusps and origins of the coronary arteries. Also

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Table 1 Patients with truncus arteriosus malformation

Case	Age race sex	Interatrial septum	Intervent septum	Truncus valve cusps	Cusp of origin of PT	Side of aortic arch	% valve overrides the R1	Diameter	
								Aorta mm	PT mm
<i>Interrupted sixth aortic arch (absent ductus arteriosus)</i>									
1	17Y WM	PFO	VSD	R LA	L	L	50	32	20
2	5W WF	I FO	VSD	R PL	L	R	75	09	05
3	12D WM	PFO	VSD	R LA	A	R	60	11	08
4	3M WF	NL	VSD	R PL	L	L	50	08	07
5	16Y BM	I FO	VSD	R PL	R †	H	60	12	06
6	12D WM	P I FO	VSD	R PL A	A	L	70	10	04
7	8D WM	PFO	VSD	R PL A	A	L	50	08	03
8	6W WM	PFO	VSD	R I LA	L	L	30	14	09
9	2Y WM	PPFO	VSD	R LA	L	L	75	23	07
10	13D BF	PPFO	VSD	R LA	A	L	85	08	00
11	5W WM	PFO	VSD	R PL A	L	L	65	11	00
12	3M WM	PPFO	VSD	R PL A	A	L	50	14	08
13	2D WM	ASD	CANAL	R PL	L	L	100	08	06
<i>Uncertain status of ductus arteriosus</i>									
14	1M WF	ASD	VSD	R PA	A	L	90	?	?
15	12Y BM	NL	VSD	R PL	L	L	25	22	19
16	16Y WM	NL	VSD	R PL	L	L	75	?	?
<i>Ductus arteriosus present</i>									
17	4M WF	PPFO	VSD	R PL A	A	L	90	13	00
<i>Interrupted fourth aortic arch</i>									
18	1D WF	PFO	VSD	R PL A	—	—	100	04	12
19	30Y WF	PPFO	VSD	R PL A	—	—	100	22	24

Abbreviations: A = anterior; ASD = secundum atrial septal defect; B = black; H = day; F = female; L = left; M = male or months; NL = normal; P = posterior; PFO = patent foramen ovale; PPFO = probe patent foramen ovale; PT = pulmonary trunk; R = right; R1 = right ventricle; SB = stillborn; VSD = ventricular septal defect; W = white or weeks; Y = year.

Cusps listed in order clockwise from R. Right and left coronary arteries arise from the corresponding anuses. Hyphen indicates the position of a raphe.

† See description in Results section.

recorded were the status of the interatrial septum, the foramen ovale and the ductus arteriosus. A computer program written in FORTRAN IV computer language and implemented on the IBM 360/148 computer at the Information Systems Department of The Johns Hopkins Medical Institutions was used to tabulate the specific anatomy of each case of truncus arteriosus malformation and the associations with other significant congenital cardiac lesions. The implied relationships among 288 observational and combinatorial statements tabulated for each heart were expressed in symbolic logic.<sup>12</sup> We employed additional statements and relationships expressed in symbolic logic to construct the sequence of normal human cardiac development as determined from embryologic studies<sup>13</sup> and to compare hypothetical embryonic pathways

postulated by the three theories of pathogenesis of truncus arteriosus malformation. For each pathogenetic theory our analysis determines the number of primary events or spontaneous deviations from normal development, required to explain the lesions observed in each patient. We used the proposition that the most efficient and probably the best explanation for a malformation complex is that theory which explains most lesions as secondary events and thus accumulates the fewest primary events. Comparison of theories was made statistically with the chi square goodness of fit test.

## Results

The 19 patients in this study were divided into four groups on the basis of the anatomy of the aortic arch (Table I). Two patients showed sixth

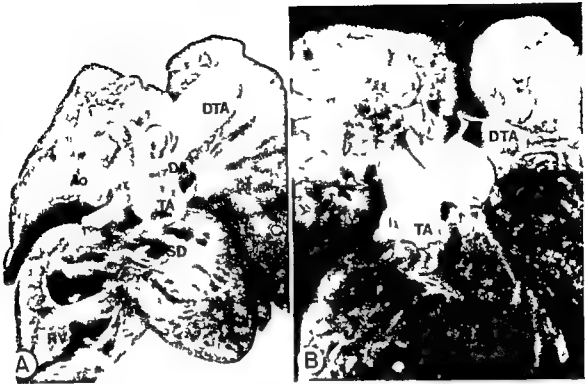


Fig 1 A and B Case No 18 with an interrupted fourth aortic arch. The descending thoracic aorta (DTA) arises from the widely patent ductus arteriosus (DA). The pulmonary arteries arise from the truncus arteriosus (TA) as does the ascending aorta (Ao) which gives origin to the great arteries. The distal aortic arch is absent. B Case No 11 with an interrupted sixth aortic arch. The pulmonary arteries arise just above the truncal valve. The ductus arteriosus is absent. I/V = inter-ventricular septum. RV = right ventricle. VSD = ventricular septal defect.

arch dominance with an interrupted aortic arch while the remainder showed dominance of the fourth aortic arch (Fig 1). The relative diameter of the aortic and pulmonary trunks were in keeping with the arch dominance—in other words only cases with sixth arch dominance showed a pulmonary trunk with a larger diameter than the aortic trunk, and in all other cases the aorta was the larger vessel. There were no other anatomic features which invariably distinguished sixth arch dominant from fourth arch dominant cases.

The ductus arteriosus showed complete agenesis in 13 cases and was patent in three cases including the two cases with sixth arch dominance. The status of the ductus could not be determined in the three remaining cases. The aortic arch was left sided in 14 cases and right sided in three cases. The remaining two cases were those with interrupted aortic arch.

All cases showed a ventricular septal defect. The site of origin of the truncus arteriosus over this defect varied from predominantly right ventricular in 11 cases to predominantly left

ventricular in one case. In six cases the truncus arose equally from the two ventricles. Among the 11 cases arising primarily from the right ventricle three arose exclusively from that ventricle.

The truncus valves were either tricuspid or quadricuspid in all cases. There were eight cases with quadricuspid semilunar valves, five of which had raphes between various cusps. Two of the 11 tricuspid truncal valve cases had a single raphe. Mitral truncal valve continuity was fibrous in all 18 cases in which the question was applicable. The nineteenth case had a single atrioventricular valve which was in fibrous continuity with the truncal valve. There were 10 cases with a muscular band and one with a fibrous band intervening between the tricuspid and truncal valves. The remaining seven cases showed tricuspid truncal fibrous continuity.

In all cases except Case No 14 right and left coronary arteries with normal distribution arose from the sinuses of the right and left cusps respectively. In Case No 14 a single coronary artery arose from the right sinus and gave

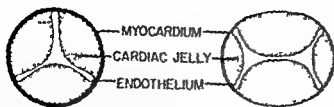


Fig 2 Diagram showing the arrangement of endocardium and cardiac jelly to be expected if the outflow tract is round or elliptical

right and left coronary arteries several millimeters distal to the ostium. The origin of the pulmonary trunk relative to the tricuspid valve cusps was also variable. In most cases the pulmonary trunk arose over either the left or the anterior valve cusp.

There were eight cases with a patent foramen ovale and six cases in which the foramen was probe patent but guarded by membrane. In three cases the septum was closed. The remaining two cases had larger atrial septal defects—one secundum type and one canal type.

The autopsy files were reviewed for documentation of associated extracardiovascular congenital anomalies. In two patients (Cases No 15 and 19) only heart and lungs were examined so the question could not be addressed. Of the remaining 17 patients five showed anomalies in other organs. Two showed cystic ovaries (Cases No 4 and 14) and in Case No 4 there was associated cytomegaly of the adrenals. Another patient (Case No 2) showed a hypoplastic left ear and focal renal dysplasia. Case No 8 had a partial DiGeorge syndrome with absent parathyroid glands, thymic hypoplasia and poorly developed T cell regions of lymphoid tissue as well as angiod changes in the lymph nodes and a patent urachus. Finally Case No 13 whose cardiac anomalies are described in greater detail below showed unilateral renal agenesis, unilateral duplication and islet cell hyperplasia and hypertrophy.

Two patients were of special interest. Case No 13 was a 3 day old white male product of a 36 to 37 week gestation who presented with respiratory distress syndrome at birth. Examination of the umbilical cord revealed a single artery and vein. In addition to the truncus arteriosus malformation and the extracardiac anomalies described above the heart showed a primitive atrioventricular canal defect including a septum primum

defect and a large canal type ventricular septal defect (19).

Case No 5 was a 16 year old black male with marked growth retardation and exercise intolerance who died of cerebral abscesses. All congenital anomalies found at autopsy were in the cardiovascular system. The truncus arteriosus arose equally from the two ventricles and gave rise directly to a small stenotic right pulmonary artery. There was a small outpouching of the truncus in the region of the expected left pulmonary artery but this vessel was absent with the left lung supplied by the bronchial circulation only. There was also a right sided aortic arch.

## Discussion

Embryonic reconstruction studies by DeVries and Saunders' and Goerttler's glass models" support the hemodynamic theory of normal cardiogenesis and the development of the spiral course of the great vessels leaving the two ventricles. The relative orientations of the two ventricles in the normal heart (left posterolateral to right) and the sequential bendings of the heart loop are the key factors in creating two spiral outflow streams which enter the two great vessels. Right ventricular outflow enters the sixth arch preferentially while left ventricular outflow is directed into the fourth arch.<sup>1,2</sup> Septa arise from the deformable cushion material in areas of low flow between these two streams and partition the ventricles semilunar valves and great vessels.<sup>1,2</sup>

Study of a 23 mm human embryo with truncus arteriosus malformation" provides direct support for the concept that a defect in placement of the cardiac chambers which redirects the normal ventricular outflow patterns may lead to abnormal cardiogenesis with failure of septation of the ventricular outflow tracts, the semilunar valves and the great vessels leaving the base of the heart. Due to abnormal relative ventricular positions the two ventricular outflow streams fuse at the semilunar valve level rather than spiraling about one another. In the presence of this fused stream there is no region of low blood flow into which the outflow tract cushions can protrude fuse and form the muscular septum which in the normal heart lies between the aortic and pulmonary valves. The end result is a single great vessel leaving the base of the heart with a single semilunar valve and in essence a single ventricular outflow tract (two tracts connected by a ventricular septal

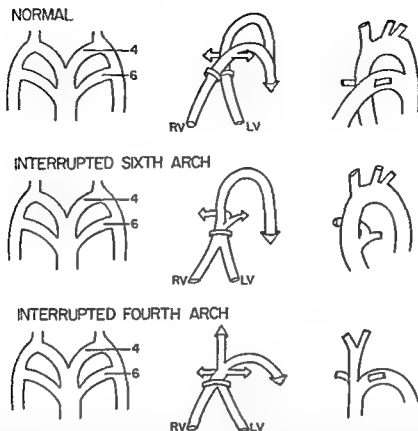


Fig 3 Diagram of bilaterally symmetrical aortic arches (left) pathways of blood flow from the ventricles into the arches (center) and the arrangement of blood vessels found after obliteration of the unused channels (right). In the normal (top) the ventricular ejection streams are separate. In the two forms of truncus arteriosus malformation the ventricular ejection streams fuse and prevent septation of the interventricular communication: semilunar valves, and proximal aortic sac. In sixth arch interruption (middle) the predominant direction of the fused outflow stream is into the fourth arches. In fourth arch interruption (bottom) the fused stream of blood flow is predominantly into the left sixth arch.

defect) An alteration of ventricular positions from normal has also been illustrated in a canine embryo with truncus arteriosus malformation.

The number of truncal valve leaflets found in this series was consistently three or four. These two most common valve cusp configurations may be understood in hemodynamic terms if one postulates a slight difference in the timing of events in the two situations. In the tricuspid case fusion of ventricular outflow streams is postulated to occur before development of the four conotruncal swellings has begun at a time when the outflow tract is still round. Here the path of least resistance for the fluid stream is through the center of the tube and the configuration of least energy for the cushion material is a tricuspid one (Fig 2). In the quadricuspid case on the other hand fusion of the streams may occur somewhat

later at a time when the outflow tract has already assumed its elliptical shape. In a tube of this shape the flow pattern of least resistance is not a cylinder through the center but itself tends to be more elliptical. Simultaneously the cushion material assumes the configuration of lowest energy which in this case is a quadricuspid configuration. Due to the fused ventricular outflow stream however the opposing conotruncal swellings are unable to fuse because there is constantly some central flow between them.

Since the presence of a single trunk leaving the base of the heart allows extensive communication between systemic and pulmonary circulations it is apparently unnecessary for the ductus arteriosus to persist during fetal life in cases of truncus arteriosus. In fact most cases of truncus arteriosus show agenesis of the ductus arteriosus.

the fourth aortic arch is well developed. There are only a few cases amounting to less than 10% in which the ductus is patent despite a well developed aortic arch. In our series of 19 cases only the two cases with sixth aortic arch dominance and a single case with fourth arch dominance had an associated patent ductus arteriosus. A smaller number of cases, 14 to 25% in other series<sup>1,2</sup> and approximately 10% in our study show interrupted aortic arch with persistence of the left sixth arch or ductus arteriosus. The more frequent finding of fourth aortic arch development and sixth arch absence implies that the single fused ventricular outflow stream is most often angled toward the fourth arch rather than the sixth (Fig 3). In a limited number of cases however, the reverse must be true. The cardiac anomaly of interrupted aortic arch itself is frequently associated with other intracardiac anomalies which shunt blood from the left to right side of the heart.<sup>3,4</sup> Since the right ventricular outflow normally enters the sixth aortic arch preferentially in these cases the sixth arch is kept widely patent while the fourth receives subnormal flow. If these flow patterns are set up before Carnegie Stage 17 (approximate ovulation age 35 days and crown rump length 12 mm)<sup>5</sup> it is possible that the fourth aortic arch may disappear completely.<sup>6</sup>

The situation in truncus arteriosus malformation is somewhat more complex than in interrupted aortic arch since we are dealing with a single outflow stream. Thieme and co-workers<sup>7</sup> have commented on the right ventricular origin of the truncus in several cases with sixth arch dominance both in their report and in the literature. However as our study suggests this is not a universal finding and multiple cases of fourth arch dominant type both in the literature and in our study have right ventricular origin. In the embryo with truncus arteriosus malformation<sup>8</sup> the fused stream was directed toward the fourth aortic arch as must be the case in the majority of truncus arteriosus cases. It is not hard to imagine however that a slightly different ventricular orientation might also lead to a fused outflow stream tilted at an angle to favor flow to the sixth aortic arch over the fourth.

There are three major theories which explain the pathogenesis of truncus arteriosus malformation: fusion of outflow streams as discussed

above; absence or hypoplasia of conotruncal ridges and absence of the pulmonary conus. The anatomic abnormality in the truncus arteriosus malformation consists of a defect in separation of the outflow tract, the valve and the great vessels. The fusion of outflow streams theory accounts for failure of septation of these three areas in terms of a single primary event namely the undivided stream of blood. On the other hand, theories which involve the absence of conotruncal ridges or the pulmonary conus require at least two primary structural defects to account for the nonseparation of the three anatomic regions. In evaluating the relative superiority of the three pathogenetic theories however, it is also important to consider the associated malformations. We employed a computer program with a symbolic logic translation of the three pathogenetic theories of truncus arteriosus malformation to tabulate the associated anatomic cardiovascular lesions unexplained by each of the theories. None of the theories explains the occasional extracardiovascular anomalies: atrial septal defect, patent foramen ovale or atrioventricular canal defect.

The theory of absence or hypoplasia of the conotruncal ridge appears to explain all other associated cardiovascular anomalies with the exception of the two aortic arch anomalies: interruption of the aortic arch and right aortic arch. A bicuspid tricuspid or quadricuspid valve may be explained as follows. A bicuspid valve occurs when the truncal swellings or the intercalated valve swellings do not develop at all; a tricuspid valve results when one of the four valve swellings fail to develop completely; a quadricuspid results when all four swellings develop but are hypoplastic and fail to fuse. Absence of the ductus arteriosus is explained hemodynamically in terms of disuse obliteration. In the face of a direct left to right communication in truncus arteriosus during fetal life the persistence of the ductus arteriosus is superfluous. Proponents of the absence of conotruncal ridges theory consider the great vessel malformations as separate anomalies requiring separate developmental events and they do not attempt to explain either interrupted aortic arch or right sided aortic arch in terms of the primary hypothesis.

The theory of absence of pulmonary conus suggested by Van Praagh and Van Praagh explains the bicuspid and tricuspid truncal valves

but the quadricuspid valve requires the additional primary event of incorporating a remnant of pulmonary leaflet. This theory incorporates great vessel anomalies as part of the malformation and in fact emphasizes the significance of the interrupted aortic arch variant although its pathogenesis is not explained in detail. The absence of conotruncal ridges and absence of pulmonary conus theories are fundamentally defective blueprint theories while the fusion of outflow streams theory is a hemodynamic theory.<sup>11</sup>

The theory of fusion of outflow streams suggested previously<sup>11-14</sup> has been discussed in greater detail above. This theory's explanation of formation of both tricuspid and quadricuspid valves is presented above and depends upon the precise timing of fusion of the ventricular outflow streams. The fusion of outflow streams theory explains associated abnormal findings in the great vessels in terms of the angle at which the fused ventricular outflow stream leaves the base of the heart. The initiating event may be either a delay in growth and closure of the endocardial cushions in relation to caudal descent of the heart<sup>14</sup> or abnormal relative ventricular orientations.<sup>1</sup> In either case the hemodynamic events following upon each explain both the truncus arteriosus malformation itself and the associated anomalies in the great vessels.

In summary explanation of the pathogenesis of truncus arteriosus malformation by either the absence of conotruncal ridges or the absence of pulmonary conus theories would require two separate primary events. In contrast the fusion of outflow theory requires only a single primary event. All three theories fail to account for interatrial septal defects and for a canal type ventricular septal defect. All theories successfully account for the tricuspid truncus valve and agenesis of the ductus arteriosus. Without additional primary events the absence of conotruncal ridges theory fails to account for interrupted aortic arch while the absence of pulmonary conus theory fails to account for the quadricuspid truncus valve. Tabulation of these primary events for the 19 cases of truncus arteriosus malformation in the present series gives 31 for the fusion of outflow streams theory, 54 for the absence of conotruncal ridges theory, and 60 for the absence of pulmonary conus theory. The fusion of outflow streams theory is therefore statistically superior

to both the absence of conotruncal ridges and absence of pulmonary conus theories ( $\chi^2_{1df} = 6.22$ ,  $9.24$ ,  $p < 0.05$ ,  $p < 0.005$  respectively). If the eight occurrences of patent foramen ovale are neglected the results are even more significant. The smaller number of primary events required by the fusion of outflow streams theory of the pathogenesis of truncus arteriosus makes it the most attractive explanation and lends additional support to the importance of mechanical forces in normal and abnormal cardiogenesis.

### Summary

Previous explanations of the pathogenesis of truncus arteriosus malformation have emphasized absence of conotruncal ridges, absence of pulmonary conus, or fusion of ventricular outflow streams. These concepts explain the persistence of the single semilunar valve and outflow vessel but have not elucidated the significance of many associated anatomic lesions. We studied the 19 patients with truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital whose hearts were available for review. The patients ranged in age from one day to 30 years and included 12 males. All hearts showed a single semilunar valve with three or four cusps and a high ventricular septal defect. In 13 patients the aorta was larger in diameter than the pulmonary artery, and no remnant of the ductus arteriosus was present (interruption of the embryonic sixth arch). In one patient the aorta was larger than the pulmonary artery, and a small patent ductus arteriosus was present. In two patients the pulmonary artery was larger than the aorta and the aortic arch was interrupted. The remaining three cases could not be fully evaluated for the status of the ductus arteriosus and size of the great arteries. We tabulated the number of associated anatomic lesions which were unexplained by each of the three pathogenetic hypotheses. The fused outflow stream hypothesis which explains truncus arteriosus malformation as the result of a maldirection of ventricular outflow streams so that the separation of two semilunar valves is prevented was superior at the 0.05 level of significance. This concept explains the spectrum of great vessel patterns in which flow is dominant into either the sixth or fourth embryonic aortic arch, permitting early disappearance of unperfused segments of

the aortic arches and is commonly seen at autopsy as either an interrupted aorta or an absent ductus arteriosus

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## Congenital aneurysms of the left ventricle

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Most left ventricular aneurysms are seen in the adult population and are due to coronary occlusion and myocardial ischemia. Aneurysms of the left ventricle in childhood are rare and when present could be either congenital or due to weakness of the left ventricle wall as a result of ischemia or surgical incision. Only a handful of cases of true congenital left ventricular aneurysms are reported in the literature. We present here four cases and a review of the literature to outline the modes of presentation, natural history, complications, and prognosis of this unusual condition.

### Case reports

**Case history 1 T J** This child was born on August 23, 1977 with a birth weight of 7 pounds. His growth and development was normal and he was first seen by one of us (J D M) with respiratory difficulty suggestive of croup. At the age of 10 months the boy looked active, alert and healthy. His weight was 10.2 kilograms and his height was 76 cm. The heart rate was 100 per minute and regular and the respiratory rate was 22 per minute. There were no abnormal findings on examination except for the displacement of a diffuse apical impulse to the left of the mid clavicular line in the fifth intercostal space. A Grade I/VI short systolic ejection type murmur was heard in the second left intercostal space.

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A chest x-ray (Fig 1 A and B) revealed a mass at the apex of the heart that could not be distinguished from the cardiac silhouette. Fluorocopy showed this mass to contract with the heart. An electrocardiogram (Fig 2) demonstrated inversion of T waves in all the chest leads. A two dimensional echocardiogram (Fig 3 A and B) was obtained which demonstrated a separate cavity lying near the left ventricular apex and communicating with the main left ventricular cavity. The walls of this cavity seemed to contract actively. At heart catheterization the hemodynamic data were normal. Left ventriculography (Fig 4 and Fig 5 A and B) in multiple views demonstrated a large outpouching of the ventricular apical region. It contracted actively along with the contraction of the main left ventricular body. The proximal coronary arteries were normal. The patient has been followed conservatively and has remained asymptomatic.

**Case history 2 B A** This child was first seen at the age of five years for evaluation of a heart murmur. Past history revealed that the child was born on February 15, 1963 after a pregnancy that was complicated by threatened abortion at three months of gestation. Her birth weight was 7 pounds and 13 ounces. The growth and development was normal. At the age of four years she had an episode of generalized cyanosis and stiffening while at play in the nursery. She awoke promptly without any residual effects. The cause of this episode was not established and no treatment was given. Our assessment showed a normal looking alert child with a heart rate of 90 per minute and regular. The blood pressure was 80/50 mm Hg in the right arm. The abnormal findings were confined to the cardiovascular system and





Fig 1 Case 1 The chest x ray in posteroanterior (A) and left lateral view (B) showing a mass at the apex of the heart that cannot be distinguished on the cardiac silhouette. The bulge at the apex is less dense than the rest of the heart shadow. On the lateral view the posterior border of the mass is clearly demarcated.

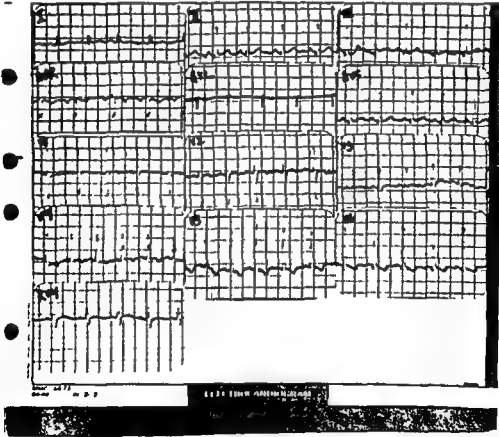


Fig 2 Case 1 The electrocardiogram showing increased voltages and inversion of T waves in the left chest leads.

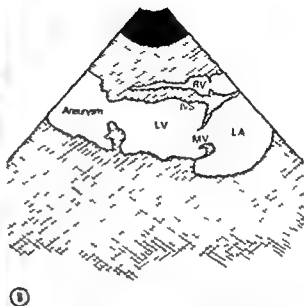


Fig 3 Case 1 Parasternal long axis two-dimensional echocardiogram (A) with accompanying schematic diagram (B) from Case 1. The aneurysmal cavity and the neck of the aneurysm are clearly seen separate from the cavity of the left ventricle proper. The echocardiogram was obtained with a Varian 3000 machine and a 2.25 MHz frequency transducer. *IVS* = Intraventricular septum. *LA* = left atrium. *LV* = left ventricle. *MV* = mitral valve. *RV* = right ventricle.

included a diffuse apical impulse outside the nipple line in the sixth intercostal space. A Grade II/VI high pitched systolic murmur was heard at the apex. The heart sounds were normal.

Chest x ray (Fig. 6) revealed cardiomegaly with normal pulmonary vascularity. The electrocardiogram was normal except for some intraventricular conduction delay and flattening of the T waves in the left chest leads. The hemodynamic data were normal on heart catheterization done shortly afterwards. Ventriculography (Fig. 7) demonstrated that extending from the left and anterior portions of the true left ventricular cavity was a very large highly trabeculated aneurysm that contracted with the left ventricular body. Proximal coronary arteries were normal.

This child did well over the next five years but electrocardiograms showed progressive inversion of T waves in the left chest leads and a heart catheterization to restudy the left ventricular function showed no significant change in its



Fig 4 Case 1 Left ventriculogram in systole showing the aneurysmal cavity separate from the left ventricular cavity proper. Part of the aneurysm is contracting in systole but the most lateral part of its wall shows no evidence of motion. There is thinning of the ventricular wall over the aneurysm.



**Fig 5** Case 1 The left ventriculogram in diastole in anteroposterior (A) and left lateral view (B) showing a fairly large left ventricular cavity and its relationship to the aneurysm. The aneurysm is extending anteriorly as well as laterally. The wall of the aneurysm is thinner compared to the wall thickness of the left ventricle. The aneurysmal cavity is trabeculated. The major coronary artery branches are normal.



**Fig 6** Case 2. The chest x-ray in the anteroposterior view shows downward displacement of the cardiac apex and resembles dilatation of the left ventricle. There is no evidence of ventricular aneurysm on the plain film.



**Fig 7** Case 2 Left ventriculogram demonstrating a large well trabeculated aneurysm of the left ventricle with significantly decreased size of the left ventricle cavity. The entire left lateral wall and apex is formed by the aneurysm. The major coronary artery branches are normal.

contractility. She was managed without surgery and when last seen at the age of 14 years she was asymptomatic, normally active and was 54 kilograms in weight and 148 cm in height.

**Case history 3 J S** This male child was born

January 6 1964 after an uncomplicated pregnancy and delivery. He had frequent upper respiratory infections in the first year of life and the chest x-ray revealed an abnormal configuration (Fig 8A). Initial physical examination was normal.



Fig 8 Case 3. Chest x ray (A) demonstrating normal heart size with a density at the left border of the heart just above the apex. The ventriculogram (B) demonstrates an out-pouching in the region of the density. This is different from the other cases in that it does not involve the apex of the ventricle but is situated higher on the anterior lateral wall. Note marked trabeculation of the aneurysm while the left ventricular cavity is normal and smooth-walled.

except for displacement of the apical impulse to the left of the mid clavicular line. The heart sounds were normal and no murmur was heard. The electrocardiogram demonstrated deep Q waves in Leads I, aVL, V<sub>1</sub> and V<sub>2</sub> and intraventricular conduction delay. A heart catheterization revealed normal hemodynamic data and ventriculography (Fig 8B) demonstrated out-pouching of the left ventricle with active contractions. This out-pouching did not involve the left ventricle apex but was mainly situated higher on the anterolateral wall. The coronary arteries were normally distributed. The child was followed at yearly intervals and demonstrated normal growth and development. Subsequently he developed fatigue, dyspnea and pallor after walking around without any significant change in the x-ray or electrocardiographic findings. At the age of two years and two months he underwent open heart surgery and the surgeon described a large broad-based out-pouching of the left ventricle presenting in the angle between the anterior descending and the circumflex coronary arteries. It measured about 3 cm in diameter at its base. There seemed to be paradoxical motion in one portion of this structure. It was thin-walled in some areas and coursing across its cavity and particularly in the region of its orifice were numerous fine filmy trabeculations. This aneurysm was then removed. The left ventricular

endocardium appeared normal in appearance but the endocardial surface of the aneurysm was white with fibroelastosis.

His postoperative course was uneventful except for a short episode of supraventricular tachycardia. A chest x-ray and a ventriculogram done four years after surgery showed the area of the previous aneurysm to be thinned and bulging minimally but the left ventricle contracted well. When last seen at the age of 16 years the patient was asymptomatic, his weight was 50 kilograms and his height was 160 cm.

**Case history 4 J O.** This child was admitted to Hennepin County Medical Center at the age of 13 months with a history of delayed development and poor use of the right side of his body. A few days prior to his admission to the hospital he had a seizure which was described as eyes deviating to the left with child becoming rigid. The patient was the product of a normal pregnancy and delivery with a birth weight of 6 pounds and 7 ounces. There were no neonatal problems. The growth and development were described as normal up to about six months of age when the mother noticed that he did not use his right upper or lower extremities well. After that his growth and development were delayed and he did not sit until the age of 13 months, had never crawled and used very few words.

His weight on admission at 13 months was 7.6



Fig 9 Case 4 Chest x ray in posteroanterior view demonstrates features similar to the ones seen in Case 1 (Fig 1). The bulge in the region of the apex is less dense than the rest of the heart. The ventriculogram (B) in the same patient shows a large aneurysm in the left ventricle apical region. The major coronary artery branches are normally distributed.

kilograms with a height of 70 cm. The pulse rate was 120 per minute with a respiratory rate of 36 per minute and his head circumference was 44 cm. The child had equal but elevated blood pressures in his arms and legs averaging 140/80 mm Hg. The neurological examination suggested bilateral Babinski sign, sustained lower left knee jerk and no grasp. The child did not respond to any verbalization or follow a light. The cardiac examination revealed a Grade II/VI murmur along the left upper sternal border but the heart sounds were of normal quality. The liver was 1 cm palpable below the right costal margin. The chest x ray (Fig 9A) revealed a prominent cardiac apex and the electrocardiogram showed an axis of  $+70$  degrees with a prolonged QRS interval and an intraventricular conduction delay with left ventricular hypertrophy. ST and T waves were depressed in the left chest leads. A left carotid angiogram revealed occlusion of the internal carotid artery and a hypoplastic extracranial portion of this artery. A heart catheterization performed a few days later showed normal hemodynamics and ventriculography (Fig 9B) showed a 3 to 4 cm aneurysmal bulge at the apex of the left ventricle. The opaque dye remained in the

aneurysm through the study. The proximal coronary arteries were visualized and appeared normal. The pressure in the left ventricle was 120/68 mm.

On cardiopulmonary bypass an ill defined left ventricular aneurysm was identified. This structure was opened, no clots were found and the entire aneurysm could not be removed since it involved both anterior and posterior papillary muscles.

A second heart catheterization was performed about a month later and left ventriculography again demonstrated a 3 to 4 cm aneurysmal dilatation of the apex of the left ventricle in which the dye did not clear as rapidly as it did in the remainder of the left ventricle. It was felt that there was persistence of the left ventricular aneurysm. The child was then seen about five months after the surgery without any significant change in his findings. About nine months after the surgery the mother found the child dead in bed. A postmortem examination was not obtained.

#### Discussion

Abbott<sup>3</sup> first described congenital aneurysm as diverticulum of the heart and these two terms

have frequently been used interchangeably. Recently a distinction has been made between a congenital aneurysm and diverticulum of the heart. The diverticulum is thought to be secondary to a developmental defect of the septum transversum, precursor of the diaphragm. It is usually a smooth-walled structure, non-contractile and involves the apex of the heart. In addition, defects of the pericardium, diaphragm and abdominal wall in the midline of the body are present.<sup>3, 4</sup> In contrast, congenital aneurysm is a well-demarcated out-pouching of the ventricular wall.<sup>5</sup> The wall of the aneurysm is usually muscular, contractile and the lumen shows numerous trabeculae as seen at operation in our Case 3. Endocardium showing a variable degree of fibroelastosis and calcification in the wall has been reported. The orifice of the aneurysm is usually close to the apex of the left ventricle but an increased incidence of congenital aneurysms with opening in the left ventricle just below the mitral valve has been described in Bantu<sup>6</sup> and Nigerian<sup>7</sup> patients.

The muscular aneurysms typically arise from the left ventricle but an origin from the right ventricle cavity has been reported.<sup>12</sup> Although ventricular aneurysms are mostly isolated defects, Carter and associates<sup>3</sup> reported an aneurysm arising from the right ventricle in a patient with ventricular septal defect and pulmonic stenosis.

**Etiology.** The embryological basis for congenital aneurysm of the heart has been discussed by several authors,<sup>13-15</sup> but there is no general consensus. It is postulated that in fetal life the ventricular wall might give way at a point of weakness.

The acquired causes of left ventricular aneurysm include origin of the left coronary artery from the pulmonary artery,<sup>16</sup> blunt trauma to the chest,<sup>17</sup> tuberculous<sup>18</sup> or mycotic<sup>19</sup> myocardial infection, postoperative cardiac surgery<sup>20</sup> and mucocutaneous lymph node syndrome.

**Presenting signs and symptoms.** The patient with congenital ventricular aneurysm usually is asymptomatic and the defect is suspected if the cardiac silhouette is abnormal on chest x-ray as it was in our first two patients. An abnormal electrocardiogram, symptoms of congestive heart failure and tachyarrhythmia may lead the patient to seek medical advice. Some patients may be seen with neurological complications secondary to

thromboembolic phenomena as was the case described by Vazquez and associates<sup>21</sup> and our fourth patient.

Bacterial endocarditis and mitral regurgitation<sup>22</sup> may be the mode of presentation and the latter does not seem to be related to any specific etiology of the left ventricular aneurysm but is rather a function of time indicating a long-standing lesion. Most of the cases described have presented with sudden death due to rupture of the aneurysm.<sup>1, 13, 14</sup> There are at least three reports in the literature of successful repair of a ruptured left ventricular aneurysm.<sup>23, 24</sup> The reason for the rupture is not clear but it has been postulated to be due to the development of excessive pressure in the lumen of the structure. The ventricular contraction that precedes the contraction of the wall of the aneurysm occludes the opening of the aneurysm in the left ventricular cavity and the subsequent contraction of the aneurysm is against a closed orifice.

**Diagnosis.** Provided it is known that malformation occurs, the diagnosis can be supported by x-ray fluoroscopy, electrocardiography, echocardiography,<sup>25</sup> radioisotope scanning<sup>26</sup> and can be confirmed by ventriculography.

A similar x-ray picture can be produced by a pericardial cyst or a mediastinal tumor. The electrocardiogram is usually normal in these two conditions while it is invariably abnormal though nonspecific in patients with congenital left ventricular aneurysms. Experience with radioisotope scanning and echocardiography is as yet limited and ventriculography though invasive is the only means of definite diagnosis at this time. As more experience is gained with the two-dimensional echocardiogram, this noninvasive procedure can be used not only to diagnose this lesion but also to follow its progression.

Ischemic ventricular aneurysm secondary to anomalous origin of the coronary artery or mucocutaneous lymph node syndrome are poorly demarcated and can be easily differentiated.

**Natural history and treatment.** The natural history of congenital ventricular aneurysm is not known in asymptomatic children; therefore the place for surgical treatment in asymptomatic cases with uncomplicated lesions is not known and a review of the literature does not give us a definite answer. We elected to wait and watch our two asymptomatic children and operated on our two symptomatic patients. The causes of symp-

toms in our third patient could not be clearly related to the ventricular aneurysm

The treatment of choice with any of the above mentioned complications is surgical. It is evident that surgical treatment may be difficult as there is no clear-cut demarcation between the ventricular and the aneurysmal tissue. It is essential that the size of the ventricular cavity proper must be assessed to be adequate and the course of the coronary arteries must be well demarcated prior to surgical removal of the aneurysm.

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## Transverse midventricular disruption after mitral valve replacement

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Between 1975 and 1977 while the risk of coronary bypass and aortic valve surgery in our experience was 1.1% and 3.5% respectively our hospital mortality rate for mitral valve replacement remained 7.5%. There were 294 patients including 48 with multiple replacements and 18 with mitral regurgitation resulting from coronary disease. The major cause of death was a newly recognized problem. Transverse midventricular disruption (TMD) was found in seven autopsied cases clinically suspected in three others and successfully repaired in one case. Clinical presentations were (1) refractory left ventricular dilatation and failure appearing at the time of removal from bypass or soon afterwards (four cases) (2) severe myocardial failure closely followed by midventricular rupture Type II of Treasure and colleagues (two cases) (3) completely unheralded midventricular rupture 3 hours and 4 days postoperatively (two cases). The pathology in all three types was basically the same. In an effort to

understand this complication we closely analyzed our operative techniques and made careful pathological studies. Because fixation petrified myocardial consistency and hides potential planes of movement gross observations were usually recorded on movie film. Microscopically both transverse and longitudinal sections were made the latter providing the most important information.

The first question was whether the problem entirely new. Review of earlier data suggested that the incidence had at least increased though incomplete forms (one half of our group) might have been previously missed. Thus we considered the obvious changes which had occurred during the study period. These included an older patient group, the introduction of the Hancock valve and the use of potassium and cold induced cardioplegia for myocardial protection.<sup>1-3</sup>

Incomplete rupture has been known to produce false aneurysm but has not been recognized as a cause of the acute and profound left ventricular failure which occasionally follows mitral valve replacement. Complete rupture is a well known complication comprising 2% of Bjork and associates' series and 0.5% of the series of Zacharias and co-workers.<sup>4</sup> The majority have occurred at the mitral annulus which was not involved in any of our group. The midventricle was thought to be the site of rupture in only 12 of the 34 previously reported patients.<sup>1-4</sup> Explanations offered for this problem have included (1) cutting too deep a plug and buttonholing the ventricle during excision of the papillary muscle in a fragile atrophic mitral ventricle,<sup>1-4</sup> (2) dissection of blood into the papillary muscle wound (3) trauma

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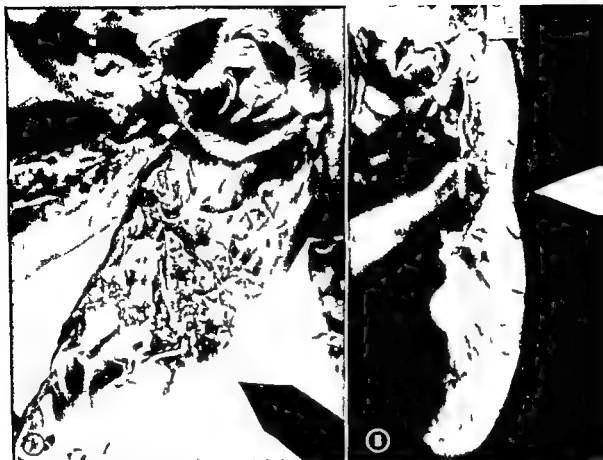


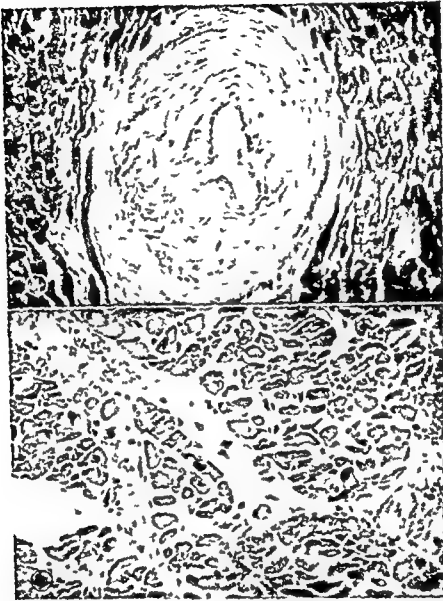
Fig 1 Case 1 A Death 3 days after TMD The macerated and thinned area above the posterior papillary site was actually two partial thickness tears which could be re approximated restoring full thickness of the wall B Lateral view of thinned area Hancock struts are well above the tear

ma from apical venting<sup>5</sup> (4) epicardial adhesions<sup>6</sup> (5) impingement of a valve strut<sup>6</sup> (6) intrinsic myocardial disease<sup>7</sup> and (7) interruption of continuity between papillary muscle and mitral annulus Our findings revised and augmented this list suggesting that an interplay of factors may be necessary to produce TMD

#### Case reports

**Case 1** A 61 year old woman with rheumatic heart disease had been symptomatic for 12 years with atrial fibrillation episodic pulmonary edema and progressive right sided failure Cardiac catheterization showed a mitral gradient of 20 mm Hg moderate mitral regurgitation and huge left atrium The cardiac index was 2.8 L/min/m<sup>2</sup> the left ventricular ejection fraction was 60% with an end diastolic pressure of 5 mm Hg The coronaries were normal At operation in December 1975 there was severe chordal resorption so

that the papillary muscles were pulled close to the mitral annulus The anterior leaflet was in abnormally high position and perpendicular (rather than normally tangential) to the plane of its chordae The patient was maintained on cardiopulmonary bypass at a temperature of 28°C Local cooling with iced saline was also used With the heart fibrillating the aorta was cross clamped for three periods totaling 36 minutes The mitral valve was replaced with a No 29 Hancock prosthesis Venting was accomplished by means of a Foley catheter placed transmitrally no suction tip ever entering the ventricle Defibrillation was uneventful But a few minutes after the heart was allowed to fill it dilated and never pumped satisfactorily thereafter ST elevation suggesting high lateral myocardial infarction persisted for 24 hours until left bundle branch block and pulmonary edema appeared on the second postoperative day Despite increasing



**Fig 2** Case 1 *A* Obstructive intimal changes involved most arteries in the papillary muscles and their root systems, but spared the adjacent ventricle even the area of the tear *B* Widened spaces between transversely running fibers. Marked sarcolysis with many myocardial nuclei lying free. This longitudinal section was taken 0.7 cm above the tears, where the muscle grossly appeared normal.

pharmacologic support and use of the balloon pump peripheral pressures fell and the left atrial pressure hovered at 30 mm Hg. Death occurred at 72 hours. At postmortem examination the heart weighed 460 gm, the coronaries were free of atheroma and none had been ligated. The heart had not ruptured. But the left ventricle which was 11 cm in thickness at the base abruptly thinned just above the papillary muscles to as little as 0.5 cm in a transverse band 1.4 cm wide

and 4 cm long. Inspection of the endocardial surface showed two roughly parallel partial thickness tears each of which was opened out flat leaving a zone of intact endocardium in between (Fig 1). Full thickness of the myocardium and endocardial continuity could be restored by pushing together these myocardial pleats. But without being held they reverted to their old open flat state implying that the separation had been present for some time probably since operation



Fig 1 Case 1 A Death 3 days after TMD. The macerated and thinned area above the posterior papillary site was actually two partial thickness tears which could be re approximated re tearing full thickness of the wall B Lateral view of thinned area Hancock struts are well above the tear

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#### Case reports

**Case 1** A 61 year old woman with rheumatic heart disease had been symptomatic for 12 years with atrial fibrillation, episodic pulmonary edema and progressive right sided failure. Cardiac catheterization showed a mitral gradient of 20 mm Hg moderate mitral regurgitation and huge left atrium. The cardiac index was  $2.8 \text{ L/min/m}^2$ ; the left ventricular ejection fraction was 60% with an end diastolic pressure of 5 mm Hg. The coronaries were normal. At operation in December 1975 there was severe chordal resorption so

that the papillary muscles were pulled close to the mitral annulus. The anterior leaflet was in abnormally high position and perpendicular (rather than normally tangential) to the plane of its chordae. The patient was maintained on cardiopulmonary bypass at a temperature of  $28^\circ \text{C}$ . Local cooling with iced saline was also used. With the heart fibrillating the aorta was cross clamped for three periods totaling 36 minutes. The mitral valve was replaced with a No. 29 Hancock prosthesis. Venting was accomplished by means of a Foley catheter placed transmurally with no suction tip ever entering the ventricle. Defibrillation was uneventful. But a few minutes after the heart was allowed to fill it dilated and never pumped satisfactorily thereafter. ST elevation suggesting high lateral myocardial infarction persisted for 24 hours until left bundle branch block and pulmonary edema appeared on the second postoperative day. Despite increasing



Fig 4 Case 3 A A double transverse tear leaves a large pseudo trabecula and extends forward into the septum. The lower tear touches the margin of the closely cut posterior papillary stump (P) (here pulled forward and seen from above). Endocardium medial to the top of the anterior papillary stump (A) has apparently been surgically nicked. Ventricular wall "hyperextended" to show the full extent and depth of the tear. B Longitudinal section of papillary muscle showing patchy, often cross-banded fibrosis perpendicular to the fiber axis and attributed to stretch myocardiopathy, as the result of severe chronic mitral prolapse. In many sections the fibrosis was more diffuse.

site'. But internally there was an extensive 4.5 cm endomyocardial tear beginning 0.2 cm above the tip of the anterior papillary muscle, extending transversely along the free wall of the ventricle and passing 1 cm above the posterior papillary muscle into the septum. Both papillary muscles were intact and microscopically showed no significant abnormalities. The closest Hancock strut was 1.2 cm from the tear. Anteriorly the plane of the surgical incision of the chordae tendineae was in line with the break in the adjacent myocardium with only a few millimeters clearance, suggesting the possibility of an inadvertent surgical nick. In many parts of the lesion blood had dissected almost completely through the ventricular wall, restrained only by the thin external

longitudinal muscle layer which had parted in the area of complete rupture. Microscopic examination indicated that the tear had developed mostly along a natural plane of transverse cleavage: vertical trabeculation above the lesion was rather well developed but virtually ended just above the papillary muscles where the trabecular roots, turning as much as 90 degrees, plunged outward through the thick middle layer of circumferential muscle bundles (Fig 3). The tear generally followed the inferior margin of these "plunge fibers" with no cellular reaction, although some inner parts were lined with fibrin, suggesting that the process may have begun earlier than was clinically apparent. There was also considerable microscopic hemorrhage along

plunge fibers as much as 14 cm above and 08 cm below the tear

**Case 3** A 69 year old woman found to have a heart murmur on routine examination developed congestive heart failure and atrial fibrillation 3 years later. At cardiac catheterization the wedge pressure was 23 mm with a V wave of 30 and a very large left atrium. The left ventricular end diastolic pressure was 12. Mitral regurgitation appeared severe with a regurgitant fraction of 0.42 despite this unloading the left ventricular ejection fraction was only 40%. The cardiac index was 1.4 L/min/M. The coronary arteries appeared normal. There was very severe mitral annular calcification. At operation in May 1976 both leaflets were aneurysmal, myxoid and obviously chronically prolapsed—judging from the perpendicularity of chordae to the leaflet plane. While the chordae were long none was broken. This appeared to be an example of severe chronic mitral prolapse leading to calcification and dilatation of the mitral annulus with the mitral regurgitation probably aggravated by selective papillary muscle failure.<sup>11</sup> The patient was maintained on cardiac bypass at 28° C, aortic cross clamping for 45 minutes was required. Intra aortic perfusion of potassium solution and both epicardial and endocardial cooling with iced saline were employed for myocardial protection. The left ventricle was vented transmitrally with a soft plastic cannula and no suction tip was ever placed in the ventricle. As cardiac bypass was diminished the patient's left ventricle failed to muster enough pressure to open the aortic valve and she could not be weaned from the pump. At postmortem examination the heart was unusually flabby and weighed 490 gm with left ventricular hypertrophy. There was no external sign of rupture but a complex and deep endomyocardial tear (Fig 4A) spiraled 6.5 cm posteriorly from a point close to the base of the anterior papillary muscle along the free wall of the left ventricle and thence into the septum where it arched superiorly. A lower tear began in the posterior papillary groove and continued even farther into the septum where it neatly divided the smooth and trabeculated portions leaving a furrowed surface of exposed muscle bundles. Posteriorly the tears produced a large free standing bundle which resembled an elegant anatomic dissection. Here vertical trabec-

ulation was virtually absent and the lesions appeared to follow natural circumferential creases. Longitudinal compression closed the cleavage planes completely, virtually concealing them. Hyperextension of the ventricle opened the tears and revealed several fine branches at both ends which could be extended with minimal tension. It looked as though the heart had simply come apart. Microscopically there was evidence of a diffuse process: dilatation and focal rupture of intramural venous sinusoids and separation of transverse fiber bundles throughout the free wall of the left ventricle and the involved part of the septum. The findings sometimes obvious as much as 2 cm basal to the tear. Also 1 to 2 mm pools of hemorrhage were noted along the inner walls of the papillary muscles and around the intramural extensions of their root systems. Although the papillary muscles appeared grossly normal microscopically on longitudinal sections there was severe predominantly cross banded fibrosis with no significant involvement of the myocardium elsewhere (Fig 4B). The nearest distance from valve strut to tear was 1.8 cm. Posteriorly the lower tear was directly in line with the stump of the posterior papillary muscle which had been resected very close to the ventricular wall (Fig 4A). While it seemed possible that a minor surgical nick had opened a natural plane of cleavage, this seemed an insufficient explanation for the extensive upper tear or the diffuse microscopic lesions. A portion of the anterior papillary muscle had also been closely resected and in the immediately adjacent ventricular wall there was a superficial cut 0.8 cm long which however did not connect with any part of the tear.

**Case 4** A 72 year old male was asymptomatic and normotensive until 8 weeks before admission when after a febrile illness he developed pulmonary edema and a pansystolic murmur. Temporary pacing was used because of complete heart block. Upon admission he was in sinus rhythm with a blood pressure of 110/80, a Grade III apical pansystolic murmur and a loud premature S<sub>1</sub> heart sound. After the administration of diuretics the neck veins were normal but the chest x ray showed interstitial pulmonary edema and marked cardiomegaly. At catheterization the pulmonary artery pressure was 80/28. There was severe mitral regurgitation associated with marked annular dilatation and calcification. The left

ventricular end diastolic pressure was 13 rising to 32 after contrast medium injection. Cardiac index was 2.1 L/min/M. The ejection fraction appeared to be fair. Coronary arteries were normal. The ECG showed right bundle branch block with a PR interval of 0.24 seconds. At surgery in June 1976 a No. 33 Hancock valve was inserted and a permanent epicardial pacemaker was left in place. There was rupture of two chordae to the medial portion of the middle scallop of the posterior leaflet. Both leaflets were aneurysmal thickened and severely prolapsed with stiffly perpendicular chordae attesting to the chronicity of the process. Microscopically there was severe myoid degeneration. The severity of the mitral regurgitation appeared as much due to the chronic leaflet disengagement, papillary muscle failure and annular dilatation as to the moderate recent chordal rupture.<sup>11</sup> A total of 67 minutes of aortic occlusion time was needed during which the heart was protected with local cooling. Potassium cardioplegia was not used. No suction tip ever entered the left ventricular cavity which was vented transmittally with a soft plastic tip. Postoperatively there was immediate hemodynamic improvement. The heart came off bypass requiring no inotropic support. The patient's course was quite smooth until 4½ days postoperatively when feeling well and sitting in his chair he suddenly exsanguinated. At postmortem the left thorax and mediastinum were full of blood. The heart weighed 750 gm with marked thickening and dilatation of the left ventricle and atrium and no coronary ligature. The area of the epicardial break was initially overlooked being only a small vertical slit 0.4 cm long. The papillary muscles though quite large were grossly unremarkable. Yet longitudinal sectioning revealed diffuse fibrosis which in less severe areas was of the cross banded type and largely spared the underlying ventricle.<sup>12</sup> Just above the papillary muscles there were two transverse tears totalling 6 cm in length neither less than 2 cm from the nearest Hancock strut (Fig. 5). The deepest tear almost avulsed the anterior papillary muscle followed by plunge fibers from the papillary groove through to the epicardial surface and was responsible for the external rupture. About 3 mm of intact trabeculation separated this from a more superficial transverse tear just above the tip of the posterior papillary muscle. Here on quick



Fig. 5 Case 4. Sudden TMD 4½ days after mitral valve replacement. Torn surfaces fresh, glistening without fibrin or necrosis. Discrete tears above both posterior (P) and anterior (A) papillary muscles with 3 mm intact trabeculation between. Anteriorly the ventricle separated just beneath a broad sheath of plunge fibers which directed the tear through to the epicardium.

inspection it was easy to mistake exposed muscle bundles for normal trabeculae. Some apparently sturdy vertical trabeculae had been broken but at their bases where they terminated in the tear area. Both papillary muscles were free standing, none had been resected and there was wide clearance from the adjacent left ventricular wall. Microscopically localized to the posterior papillary ventricular groove below the line of the tear there were small pools of edema and sarcolysis, the latter possibly dating back 4½ days to the time of surgery. The torn surfaces themselves showed no necrosis and very little fibrin deposition, implying that the break had been sudden and agonal. Thus it appeared that ruptured chordae had complicated the course of cardiomyopathy associated with long-standing mitral prolapse and its secondary effects on the mitral



Fig 6 Case 5 TMD in a patient with rheumatic heart disease. The Hancock struts are unusually close to the edge of the tear. Surgical repair was unsuccessful because only the outer layers were approximated and then only in the area of the external break.

annulus and papillary muscle. Perhaps anlage for TMD in this case may have resembled the pools of fiber separation and sarcocystis seen in the papillary groove. But the delay in onset of the tear, the lack of necrosis or of any structurally impressive lesions dating back to the time of surgery, and the absence of any visible source of trauma implied some sort of cumulative process.

**Case 5** A 70 year old woman with a childhood history of rheumatic fever had been diuretic dependent for 12 years and nearly bedridden for one year. On examination she had mitral systolic and diastolic murmurs, a brief blow of aortic insufficiency, isoelectric atrial fibrillation and a huge left atrium. Although she had been given

diuretics to free her from edema, the neck veins had large V waves suggesting tricuspid incompetence. Angiographically, the left ventricular size was only moderately increased. The ejection fraction was 48%, with severe mitral and a trace of aortic regurgitation. The coronaries showed minor luminal irregularities. The pulmonary artery pressure was only 28/10, probably as a result of the giant left atrium and low output. There was a 4 to 5 mm mean diastolic gradient over the tricuspid valve and marked venous unsaturation. At surgery in July 1976 the patient was maintained at 25° C and the heart further cooled with iced saline. The mitral leaflets were fused and retracted, the papillary muscles were almost absorbed into the valve. Replacement was with a No 31 Hancock prosthesis. The severe tricuspid leak was corrected by annuloplasty. At one point a suction tip introduced into the left ventricle was inadvertently wedged into the papillary groove. Yet the patient did quite well, was defibrillated with one countershock and came off bypass without pharmacologic support. Cardiac output increased from 2½ to 4½ liters with a left atrial pressure of 15 mm Hg. Twenty minutes later, during closure of the sternum, the heart suddenly slowed and distended. Lateral ST elevations were noted on the ECG but no air was seen in the coronaries. Manual cardiac massage was begun. Within a few minutes copious bleeding was noted from a tear in the left ventricular surface which appeared to be 1 cm below the atrioventricular groove near the anterior papillary site. Repair necessitated ligation of an anterior obtuse marginal coronary artery. Thereafter the ventricle never pumped adequately. The patient lived for 5 days with intensive hemodynamic support, her ECG showing lowered voltage and marked lateral ST elevation. X ray evidence of pulmonary edema did not develop but volume loading raised filling pressures without affecting systemic pressure. Reexploration excluded tamponade and showed a virtually akinetic left ventricle. In the last 24 hours right bundle branch block developed. Shortly before death thoracotomy drainage increased sharply. At autopsy there was a massive hemomediastinum with 800 gm of clotted blood. The Hancock prosthesis appeared to be well seated. The heart weighed 500 gm with no critical coronary lesions. An unusually straight and deep endomyocardial tear 5 cm long



Fig 7A Case 6 TMD in a patient with chronic mitral prolapse. A misaligned Hancock valve may have left V shaped on the septum (V) but there are discontinuous tears in each papillary groove with 12 cm of intact vertical trabeculation between. The deepest lesion is the area of apparent erosion above the anterior papillary muscle (A) which has been pulled forward. The posterior tear is hidden behind the muscle (P). Both tears were initially missed.

extended transversely from 0.6 cm above the posterior papillary tip near the septum to a corresponding point above the anterior papillary site where the area of ventricular repair was aneurysmal (Fig 6). The left ventricle was focally thinned to 0.4 cm for the entire length of the lesion. The papillary muscle tips had been conservatively resected but at a point quite close to the line of the tear. In the anterolateral wall there was fresh myocardial infarction related to the surgically ligated anterior obtuse marginal artery. Thus detailed microscopic studies were done only near the posterior papillary muscle. The surface of the tear was lined with fibrin but there was very little necrosis. The papillary stump showed a great deal of fiber separation and sarcolysis. In the basal ventricle even 1 cm posterior to the lesion thin sheets of hemorrhages following the line of dilated venous sinusoids extended almost to the epicardial surface these lesions having no direct connection with the tear itself. Vertical trabeculation was quite defective in the entire area but it was not possible to identify any obvious plane of natural cleavage. At the posterior papillary site the Hancock strut came within 2 mm of the edge of the tear and the inflow tract

appeared too small for the No 31 prosthesis. Thus it seemed quite possible that the valve strut had initiated the tear although there were no discrete strut marks and the lesion appeared too extensive to have been caused entirely by focal trauma.

**Case 11** A 76 year old male known to have a leaking valve and palpitations for 30 years suddenly developed severe congestive failure and was found to have an apical pansystolic murmur, a closely spaced S<sub>3</sub> gallop and atrial fibrillation. Cardiac catheterization after diuresis showed severe mitral regurgitation and dilatation of the left ventricle with an ejection fraction of 50%, an end diastolic pressure of 12 and no significant coronary disease. The pulmonary wedge V wave was 24, the PA pressure was 32/16 and the cardiac index was 2.0 L/min/M<sup>2</sup>. At surgery in March 1977 the mitral annulus was large, both leaflets were aneurysmal with ruptured chordae to the midportion of the middle scallop of the posterior leaflet. Pathologically there was severe myxoid degeneration and marked perpendicularity of chordae to both leaflets. It seemed probable that the patient had mildly symptomatic mitral prolapse for many years before rupturing chordae.





Fig 7B Case 6. Wide separation of transverse fiber bundles even in the untorn segment, decremental toward the base. A residue of proteinaceous fluid in the widened spaces suggested that they were not fixation artifact.

as the result of chronically increased mitral stress. A No 33 Hancock valve was inserted. Myocardial protection was afforded by profound endocardial and epicardial hypothermia as well as by potassium cardioplegia maintained during a 28-minute period of aortic cross-clamping. The procedure was uncomplicated. After defibrillation the patient went into sinus rhythm with excellent ventricular function. Ten minutes later the rate slowed requiring atrial pacing. Then with the chest nearly closed a ventricular ectopic beat on the T wave initiated ventricular fibrillation and severe acute dilatation. Although defibrillation was done almost immediately the ventricle never again contracted effectively and could not be brought off bypass even with the use of the intra aortic balloon. At postmortem the heart on external examination seemed intact. It weighed 420 gm. and was unusually flabby. There was a

separate transverse endocardial tear in each papillary muscle groove especially long and deep anteriorly. The lesions were largely concealed until the papillary muscles were pulled forward or the wall was hyperextended (Fig 7A). The two tears were directly in line with each other and were separated by 1 cm of intact vertical trabeculation which was sturdy and well rooted toward the apex. The surfaces of the lesions were irregular because of exposed muscle bundles. The prosthesis was apparently rather wide for the ventricle and had been mounted so that one of its struts faced the septum where there was a superficial V-shaped endocardial break. This however did not quite match the position of the strut. At its apex the V communicated with the tear in the posterior papillary groove. The distance from strut to tear was 0.5 cm posteriorly and 1.2 cm anteriorly. Thus while strut impingement might have initiated the posterior tear there must have been a different explanation for the independent and deeper anterior lesion. Microscopically there was marked separation of the circumferential muscle bundles greatest at the level of the papillary muscle and decremental toward the mitral annulus (Fig 7B). These changes and the extreme flabbiness of the heart resembled findings in Case 3 whose mode of death was similar. The papillary muscles also showed cross banded fibrosis and intimal proliferation of small arteries the latter not as severe as in Case 2.

Case 7. A 52 year old man suddenly developed substernal chest pain pulmonary edema shock, and a Grade II decrescendo apical systolic murmur in August 1977. Because of the absence of QRS abnormality the diagnosis of ruptured chordae was suspected. Cardiac catheterization showed occlusion of the circumflex trunk but excellent movement of the entire left ventricular wall with an ejection fraction of 70%. There was massive mitral regurgitation but little enlargement of the left atrium. The left ventricular end-diastolic pressure was 15 rising to 21 after angiography. Surgery done within 4 days of the chest pain showed that a necrotic 1 cm by 1 cm by 0.5 cm tip of the anterolateral papillary muscle had ruptured. Very likely acute ischemic loss of papillary function had resulted in sudden severe mitral prolapse which increased stress on the underlying muscle and contributed to rupture. The valve was replaced with a No 27

Hancock prosthesis and the posterior lateral obtuse marginal artery was grafted. Potassium cardioplegia and local epicardial cooling were used during the 54 minute period of aortic cross-clamping. Decompression was by transmitral venting. No suction tip ever entered the ventricle. Off bypass the patient did very poorly despite heavy catecholamine support and the intra aortic balloon pump. The ECG showed much decreased QRS voltage and marked lateral ST elevation which did not evolve. Death occurred 2 days later. At postmortem examination there was complete occlusion of the circumflex trunk but the graft was patent and the other coronaries were unremarkable. The heart weighed 780 gm. There was grossly visible infarction of the anterior papillary stump and a 15 cm area adjacent to the mitral annulus both thought to be about 1 week old. Microscopically there were also scattered foci of posterior papillary and subendocardial necrosis. A superficial transverse tear 6 cm long but only 0.3 to 0.4 cm deep extended along a line 0.2 cm above the anterior papillary muscle beyond a point 1.2 cm above the posterior papillary tip (Fig 8A). It was coated with fibrin but did not involve infarcted muscle. The tear appeared to have developed in a normal transverse crease (in an area with almost no vertical trabeculation) and to have followed a line of natural fiber cleavage which microscopically proved to be a venous sinusoid. Although the lesion appeared shallow there was microscopic evidence of TMD in a wide area.

1 From the apex of the tear the sinusoidal cleavage plane continued branching outward almost to the epicardium. In this unrealized part of the lesion the vascular channel was focally dilated and broken with loss of endothelium and microhematomas invading adjacent muscle where bundles and even individual fibers were separated and there was focal sarcolysis.

2 As much as 1 cm above the visible tear and roughly parallel to it streamer like perisinusoidal hematomas from dilated vascular channels penetrated the myocardium suggesting the potential for other breaks similar to the gross lesion (Fig 8B).

**Case 3** A 64 year old woman in December 1977 had tight severely symptomatic mitral stenosis but good left ventricular function with an ejection fraction of 60% and a diastolic pres-



Fig 8A Case 7 TMD after replacement of the mitral valve for rupture of the anterior papillary muscle in coronary artery disease. The shallow obliquely coursing tear follows a natural endocardial crease in an area of defective vertical trabeculation. Though coated with fibrin it was easily missed until the heart was hyperextended.

sure of 8 mm Hg. At surgery the mitral orifice was 10 by 0.4 cm. The valve was contracted, intra-annular and diaphragm like with severely shortened chordae tendineae. Very conservative resection was done leaving the papillary muscles full length. Potassium cardiac arrest was used and the heart was locally cooled with iced saline. A No. 27 Hancock valve was inserted although it was felt to be a snug fit. Venting of the left ventricle was accomplished through a soft catheter tip placed transmitrally. As the vent was removed after defibrillation the initial contractions appeared normal but in 1 minute the heart abruptly dilated as ST elevation developed in the lateral and later in the inferior leads. A careful search showed no air in the coronaries. TMD was

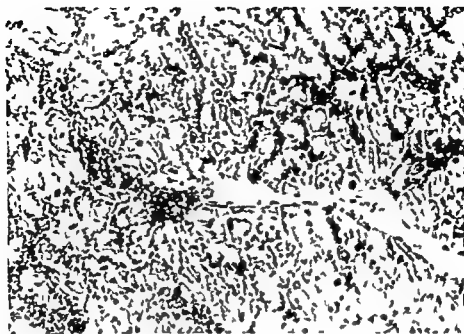


Fig 8B Case 7 One of many widened and ruptured venous sinusoids 0.5 cm deeper and 1 cm above the gross lesion

at once suspected because of the acute unaccountable power failure and the ST changes. Venting was reinstituted but external massage was not used. When bypass was finally discontinued an hour later the heart immediately ruptured from a 1.5 cm longitudinal slit in the posterior wall beginning 2 cm below the AV groove near the posterior papillary site. With the knowledge from previous anatomical studies that the internal disruption was much more extensive and perpendicular to the exit wound the surgeon used deeply placed sutures and continued the repair 4 cm laterally as far as the approximate position of the anterior papillary muscle. He ended by sewing the posterior pericardium and a knitted Dacron patch like a tamponading tent over about one third of the posterior ventricular wall, fortunately sparing major coronary branches. Even with the aortic balloon and intensive pharmacologic support there was great difficulty in weaning the patient off cardiac bypass. For the first week postoperatively she was dependent on 1:1 balloon pumping and intensive pharmacologic support. The ST elevations gradually cleared over a 60 hour period. There were never any ECG changes of transmural myocardial infarction. The echo indicated severe global hypokinesis of the left ventricle, confirmed by a sector

scan done 1 year later. The patient remains in severe chronic heart failure.

#### Summary of anatomic findings

Despite considerable variation in the depth of the tear lesions in the seven autopsied cases were remarkably similar and basically the same regardless of whether the heart had ruptured. The endocardial break always involved the free wall of the left ventricle at or not far above the papillary sites and extended 4 to 8 cm circumferentially, sometimes into the posterior septum. The orientation of the lesion was generally transverse but often it spiraled somewhat upward higher posteriorly in general following the line of circumferential muscle bundles which comprise the bulk of the left ventricular wall. In two cases the lesion tore deeply into the proximal groove between the papillary muscle and ventricle. The break was often at least partly concealed, pulling the papillary muscles forward or hyperextending the ventricle separated the planes of cleavage. In two cases there were parallel tears in one instance dissecting out a large band of the spiral cardiac musculature. In the other patient who survived partial rupture for 2 days the nature of the problem was not immediately obvious; above the papillary muscles there was a zone of circumfer-

ential thinning apparently partly denuded of intima yet intimal continuity and full thickness of the wall could be restored by folding the pleat like tears back together again. In two patients who died in the operating room the cardiac muscle was unusually flabby and edematous so that the tear could be easily extended with minimal tension. In five cases a deep and extensive tear was restrained in some areas only by the thin external longitudinal muscle layer. Eventual rupture (in three cases) parted these fibers hence the exit was always vertical and perpendicular to the inferior lesion.

The preoperative lesions varied.

1 A rheumatic diaphragm like valve with an abnormally high anterior leaflet chordal resorption and resulting stricture of the inflow tract (four cases)

2 Severe chronic mitral prolapse (three cases with chordal rupture in two)

3 Coronary artery disease with rupture of the anterior papillary tip (one case)

As we have previously pointed out disengagement of the leaflets particularly an abnormally high position of the anterior leaflet (removing the normal boundary between inflow and outflow tracts of the left ventricle) probably greatly increases sail traction on the papillary muscles and their ventricular attachments. All patients except Case 7 showed abnormal perpendicularity of chordae to leaflets the commonest anatomical expression of chronic mitral disengagement. The three patients with chronic mitral prolapse all had distinctive cross banded papillary muscle fibrosis findings not uncommon in older persons with long standing mitral valve prolapse and possibly due to stretch myopathy or microbreakage of the muscle in a plane perpendicular to the fiber axis and to the stress applied. The lesions tend to be perivascular (Fig 4 B) and could be due partly to capillary leaks. In one patient (one rheumatic and one myxoid) the papillary muscles showed unusual obliterative disease of the small coronaries (Fig 2 A) perhaps also attributable to chronic trauma.

While chronic abnormalities were common in the papillary apparatus the actual break occurred in the proximal myocardium through apparently healthy muscle with little if any necrosis even in patients who survived several

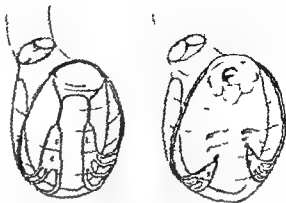


Fig 2 Schema of the "untethered ventricle" theory. After mitral valve replacement in both systole and diastole there is abnormal longitudinal traction on the left ventricular endocardium which sometimes separates along natural lines of cleavage or foci of minor trauma.

days. In five cases it was possible to show that the tear developed along natural lines of cleavage: (1) venous sinusoids (2) points at which the roots of trabeculae carneae plunge through the ventricular wall (3) transverse creases in areas of absent or scanty trabeculation. When vertical trabeculae were broken they were usually rooted in the area of the tear. In control hearts considerable variation in the amount of vertical trabeculation above the papillary sites has been noted. In some cases most of the longitudinal musculature of the endocardium is diverted into the mitral apparatus and even when present is rooted loosely or just above the papillary muscles not arranged to withstand much longitudinal stress. The two patients with the best developed vertical trabeculation between the two papillary sites (Case 4 and Case 6) had separate tears with sparing of the areas where trabeculation continued uninterrupted toward the apex.

Microscopically in many cases there was some evidence of transverse fiber disruption at some distance from the tear—the process usually decremental toward the base. These accessory lesions consisted variously of (1) dilated fractured venous sinusoids (2) hemorrhages along plunge fibers (3) wide separation of transversely running muscle bundles and sometimes of individual fibers (with sarcolemmas in those who survived for as much as 2 days). Foci of hemorrhage were also common in the papillary roots. Case 7 showed

that mid ventricular disruption even when apparently superficial (and easily overlooked) could be quite long and circumferential with microscopic evidence of a more diffuse process.

This aggregate of observations implied that TMD might be associated with abnormal myocardial stretching especially in the long axis of the heart.

## Discussion

Clinical recognition of TMD may seem all too simple once complete rupture has occurred. But even here it must be differentiated from annular separation (Type I of Treasure and colleagues<sup>1</sup>) with which we suspect it has been confused. Incomplete rupture more difficult to recognize is manifest by the sudden loss of effective left ventricular contraction usually soon after the completion of bypass. Coupled with this may be ECG changes suggesting acute high lateral and even inferior infarction. These findings should make the surgeon look carefully for coronary air embolism before diagnosing TMD. The ST changes may be due to compression of adjacent branches of the circumflex coronary artery by the intramural hematoma. But we think they are more likely caused by the pressure of dissected blood against the electrically active outer myocardial layer. The fact that ST segments can remain focally elevated for nearly 3 days (Case 8) and finally return to normal without QRS abnormalities of infarction favors the second possibility.

In trying to decipher TMD we considered a number of possible causes. While several factors seem important it appeared that a combination was usually required. The first recognition of the lesion in 1970 and its considerable incidence in the next 18 months appeared to be an important clue. The following factors were considered.

**1 A change in the type of patients admitted for surgery.** During the study period a less favorable population was submitted for mitral valve replacement including older patients and a number with severe coronary disease. Advanced age seemed to be a definite risk factor. The median age for persons dying of TMD was 65 years. Yet age was not the only explanation. Two of the patients were in their early 50s and the underlying lesions were various. As already noted anatomical studies suggested other indices of

degeneration especially in the papillary muscles. Left ventricular dysfunction however as ordinarily recognized did not appear to be a factor. End diastolic pressures had usually been normal though some cases had low ejection fractions for their degree of mitral regurgitation.

**2 Characteristics of the Hancock valve.** As we first considered the etiology of TMD the Hancock valve itself naturally came under suspicion. Temporally the relation was not altogether convincing. While the porcine valve was used exclusively after June 1974 the first case of TMD was not recognized until November 1975. Yet the 2 cm downward projection of the rather angular Hancock struts makes it important to consider the area into which they will project and to size the valve before the heart is cardioplegic. If the ventricle is small or the papillary muscle inserts close to the annulus one can visualize how damage might occur particularly if it became necessary to give external massage. In three cases the fit of the prosthesis was snug. There was however no consistent relation of strut to lesion the only predictable feature was proximity of lesion to papillary muscle. In five of our cases the struts seemed much too remote and external massage had been used in only one case. Further more ventriculographic studies have indicated to us that there is normally little basal movement of the papillary tips during ventricular contraction and the papillary tip is further separated from the mitral annulus after valve replacement. Thus it seems unlikely that the papillary muscles were shaved off as the ventricle contracted against the struts. In two cases (No. 5 and 6) a strut was close enough to part of the tear to arouse suspicion. We concluded that strut impingement was not the usual cause of TMD but that it might help initiate a tear particularly if the valve is misaligned or too large. A distinctive characteristic of the Hancock valve is its flow pattern which produces a forceful central jet. During ventriculography we have many times seen hosing of this jet often seeming to strike close to the anterior papillary muscle site. Although this in itself seems to be an insufficient source for trauma it might be additive with other factors.

**3 Unrecognized operative trauma.** Though there was reason to suspect minor trauma in four cases the types were various and the resulting lesion was always grossly disproportionate. In Case 5 (who had one of the deepest and most

extensive tears) a suction tip had been wedged in the papillary groove. In the other cases no rigid apparatus was allowed in the ventricle and venting was done transmittally with a Foley or soft plastic cannula. Inadvertent nicking of the adjacent left ventricular wall may sometimes occur during removal of the mitral valve. In each of our cases the leaflets were first detached above and then the papillary tips or chordae were cut using curved scissors. One blade of these traveling in the area between the papillary tip and the adjacent left ventricular wall might accidentally open a natural transverse plane of cleavage. In Cases 1 and 5 the clearance in this area seemed reduced. Surgical trauma also appeared to be a possible factor in Case 3 where the lower arm of a complex tear developed adjacent to a closely cut papillary stump; however it was difficult to accept this explanation for the rest of the very extensive lesion. In four other patients the papillary tips were free standing and well separated from the ventricular wall. Papillary and chordal resection except in Case 3 was conservative. There was no instance of a button holed ventricle.

**4 Stretch damage and cardioplegia.** The coincidence between the introduction of cold and potassium induced cardioplegia<sup>2</sup> and the recognition of TMD appeared suggestive. The techniques were gradually adopted during 1974 to 1976 and were used in seven of the eight cases. The anatomy of the lesion suggested stretch damage. Excessive traction on the mitral apparatus resulting in an abnormal lifting or bending of the papillary muscles seemed a good explanation for many of the pathological findings. While the surgeons were not aware of exerting any unusual force they did note that during cardioplegia the heart appeared very easily deformable. Perhaps this remarkable plasticity makes cardioplegic muscle more susceptible to inadvertent stretching. Features of the lesion compatible with this were

- 1 Involvement of the papillary groove (Cases 4 and 6)
- 2 Discontinuous tears focused over the papillary sites (Cases 4 and 6)
- 3 Diffuse microscopic lesions of the ventricular wall perhaps explainable by inward tenting of a very pliant left ventricle attached to the lifted papillary muscle
- 4 Hemorrhages in the papillary root system. Unfortunately there were difficulties with this

theory as the complete explanation for TMD. In four cases (No 1, 2, 5 and 7) the lesions were centered well above the papillary groove which probably would have been torn if papillary traction had been the chief cause. There was also the strong implication that the lesion could result from some kind of cumulative stress. In Case 4 where the anterior papillary muscle looked almost avulsed (Fig 5) rupture occurred 4½ days after operation suddenly and agonally. There was no necrosis and scarcely any fibrin on the exposed surfaces. These observations implied an additional factor contributing to abnormal stretching of the ventricle.

**5 Stretch damage and the untethered left ventricle.** Would TMD have occurred with the same intraoperative trauma or stretching if the mitral valve had been left intact? We think not. To the anatomist the mitral apparatus seems not a mere appendage of the left ventricle but an integral part of its structure. The work of Armour and Randall<sup>11</sup> implies that papillary muscle chordae and leaflets form the inner arm of a longitudinally coursing loop connected at both ends with the mitral annulus. The outer arm of this *mitral loop* is a large part of the thin superficial coat of the left ventricle which consists of longitudinal fibers fixed to the mitral annulus converging toward the apex and penetrating at various levels (as plunge fibers) through to the papillary muscles and trabeculae. Together with the mitral apparatus these outer vertical fibers appear to form a binder for the thicker circumferential myocardial core and to provide an important source for longitudinal shortening of the left ventricle. Thus detaching the papillary muscles from the annulus may be transecting a major vertical fiber loop—and also removing a longitudinal binder. One might guess that with each systole the outer long axis fibers (still attached to the mitral annulus) would tend to retract the fulcrum of the mitral loop—the base of the papillary muscle—into the left ventricular wall toward the apex increasing longitudinal stress on the remaining endocardium. During diastole loss of the mitral ring could also allow the untethered ventricle to overexpand longitudinally tending to pull apart its unbound transverse core (Fig 9). In four of our patients the left ventricular inflow tract had been structured by chronic shortening of the mitral apparatus: in three the mitral loop had probably been functionally destroyed but artifi-

cially supported by long standing mitral pro-  
lapse" and in one it had been ischemic. Perhaps  
such an area rendered cardioplegic unduly  
stretched and then suddenly untethered and  
forced to assume a new workload may acutely  
malfunction and dilate. Such a process might be  
cumulative and would explain the phenomenon  
of delayed fiber separation and rupture without  
necrosis or a visible source of trauma. This theory  
is also compatible with the other anatomical  
features of the lesion: (1) its usual location just  
proximal to the papillary muscle without neces-  
sarily involving the papillary groove; (2) its  
circumferential propagation; (3) its development  
along natural lines of cleavage; (4) the occurrence  
of parallel, complex, and discontinuous tears; and  
(5) the microscopic evidence of diffuse changes  
sometimes seen at a distance from the obvious  
lesion. Active retraction of the papillary muscle  
into the ventricular wall could explain pinching  
and rupture of blood vessels supplying its root  
system. This retraction would also explain the  
divergence of the papillary muscle sites" which  
we not uncommonly see on angiograms after  
mitral valve replacement.

The two sources of longitudinal stretch damage  
would obviously be additive. The role of cardio-  
plegia deserves further experimental study. We  
need to know precisely what effects cold or  
potassium induced relaxation have on the tensile  
properties of the left ventricle and how long these  
last after cardioplegia is apparently reversed.

#### Incomplete rupture and myocardial dysfunction

When TMD did not lead to immediate death it  
appeared to be profoundly destructive of myocar-  
dial function. While there were sometimes  
contributing factors—i.e. a small recent myocar-  
dial infarction in Case 7 and suturing of the left  
ventricle in Cases 5 and 8—pump failure in Cases  
1, 3, and 6 can scarcely be attributed to anything  
except TMD itself. All these patients had fair or  
good left ventricles preoperatively. The mecha-  
nism of dysfunction is not difficult to understand  
when the tear is very deep and extensive (as in  
Cases 3 and 5) but severe myocardial failure also  
occurred when the gross lesion was much less  
impressive. The role of myocardial edema (Cases  
3 and 6) and of more generalized microscopic  
disruption (Cases 1, 2, and 7) may be important.  
Cases 1 and 7 also suggest that some patients

could survive TMD (without benefit of diag-  
nosis) and that if it contributed to the cardiomy-  
opathy sometimes seen after mitral valve replace-  
ment the lesions viewed later would probably be  
only myocardial thinning and endocardial fibrosis  
with patchy involvement of circumferential  
fibers. In fact these have been familiar autopsy  
findings of cardiomyopathy associated with  
mitral replacement since the earliest experience  
with prosthetic valves.<sup>10</sup> The course of Case  
1 certainly also implies that cardiomyopathy can  
result from healed TMD.

#### Repair and prevention

The present anatomic observations suggest a  
better method for surgical repair when complete  
rupture occurs on the operating table. Although  
the external break appears to be small and longi-  
tudinal, the surgeon should recall that the inner  
lesion is extensive and generally transverse,  
usually spiraling slightly upward from the anterior  
or to the posterior papillary area. Repair of the  
whole lesion requires placing sutures deeply and  
securing both papillary sites. Removal of the  
valve and suturing from within may well be  
preferable.<sup>4</sup>

If the present concepts of etiology are correct it  
would appear that valvular reconstruction as  
done by Yacoub and DeGasperis<sup>11</sup> should elimi-  
nate the problem. When mitral replacement is  
necessary several measures should be important  
in preventing TMD.

1 During excision of the mitral valve careful  
avoidance of trauma to the area destined to be  
stretched after the ventricle is untethered—par-  
ticularly (a) surgical tension on the papillary  
muscles in the cardioplegic heart and (b) wide  
sized valves in small ventricles.

2 Very careful and slow weaning of the cardio-  
plegic heart from bypass to allow for return of  
normal muscular tone before the myocardium is  
subjected even to the stress of normal filling and  
ejection. At present we allow the rewarmed heart  
to pump empty for 30 minutes and then adminis-  
ter calcium chloride before even starting the  
weaning process.

3 The continued avoidance of ventricular  
distention, prophylactic use of unloading tech-  
niques for several days in high risk patients,  
despite apparent hemodynamic well being. With  
increasingly strict adherence to these principles

our operative mortality rate fell below 5% in 1977. In 1978 and in the first 6 months of 1979 there were no proven cases of TMD. The diagnosis was suspected however in one non autopsied patient in whom the weaning protocol had not been used.

In our original presentation<sup>10</sup> we also proposed that leaving the posterior leaflet intact during mitral valve replacement should reduce the risk of TMD. Our surgeons have not used this approach, suspecting that it might provide a focus for embolism. In 1964 however Lillehei and colleagues demonstrated that it was possible to insert a ball in cage prosthesis without removing the mitral valve. Their goal interestingly was to reduce postoperative left ventricular failure. Rastelli and co workers disputed this idea finding that in normal dogs studied 2 days after mitral valve replacement retention of valvular continuity made no difference to ventricular function. These observations however may not apply to old sick mitral ventricles especially during the first minutes or hours after cold or potassium induced cardioplegia. Furthermore anatomical studies by the same authors offer some evidence for the importance of preserving the mitral loop.<sup>11</sup> Retaining even partial continuity between papillary muscle and annulus was found to prevent the otherwise inevitable infarction atrophy and retraction of the papillary muscles which followed mitral valve replacement. The present study taken with a previous report on ventricular buckling in mitral prolapse<sup>1</sup> suggests that the mitral loop may be a factor in left ventricular function.

### Conclusions

Between late 1975 and 1977 transverse midventricular disruption (TMD) was our chief cause of death after mitral valve replacement. The same lesion may produce acute power failure in the operating room or cardiac rupture the latter delayed sometimes as long as 4 days postoperatively. The incidence of the problem apparently suddenly increased after the introduction of cold and potassium induced cardioplegia. Many of the anatomic features suggest stretch damage. The substrate of the lesion may be the untethered left ventricle produced by cross cutting the mitral loop. But realization probably usually requires too rapid weaning of the cardioplegic heart from

bypass and perhaps inadvertent stretch trauma to the very relaxed ventricle. Surgical nicks or strut impingement of the Hancock valve seem less important factors. Old mitrally damaged hearts appear the most susceptible TMD even when apparently mild appears to be associated with severe left ventricular dysfunction and sometimes diffuse microscopic disruption. Long term follow up in one case suggests that the lesion may be a cause of the chronic cardiomyopathy sometimes seen after mitral valve replacement. By changing our operative technique to include a 30 minute period of empty beating after reversal of cardioplegia we apparently have eliminated the fatalities. No cases have been recognized in the last year. When rupture does occur repair should take into account that the primary lesion is endocardial and above both papillary sites.

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# Experimental and laboratory reports

## Autonomic tone of patients during an electrophysiological catheterization

The role of autonomic influences on the reproducibility of sinus node function studies

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In recent years invasive techniques have been used to obtain information about the electrophysiologic properties of the human heart. These techniques of recording intracardiac electrograms and placement of intracardiac extrastimuli form the basis of the electrophysiological study which is oftentimes used to formulate therapy, determine the need for pacemaker intervention, etc. It is reasonable to assume that the electrophysiological study which is performed in a setting of x-ray units, electronic equipment, venesections, catheter punctures, and gownned personnel may induce a state of stress and apprehension in the patient. According to the theory of Cannon and data from others, the procedure should elicit a hyperadrenergic response with increased release of endogenous catecholamines. As suggested by

Strauss and colleagues<sup>1</sup> the hyperadrenergic response could modify the results obtained during the procedure, specifically decrease the basic cycle length, normalize the sinus node function studies, and mask underlying sinus node dysfunction.

This investigation was designed to determine whether the electrophysiological study induces a hyperadrenergic state, to investigate the relationship between the adrenergic state and sinus node function results, and to assess the reproducibility of the sinus node function studies.

### Methods and materials

**Patient population.** Sixteen patients were studied. The patients were divided into two groups on the basis of data derived from the sinus node function studies. Group I consisted of eight patients (mean age 51 years, six males, two females) with normal sinoatrial conduction times ( $\leq 200$  msec) and normal corrected sinoatrial recovery times ( $\leq 395$  msec). Two of the patients had atherosclerotic coronary artery disease proven by catheterization. The remaining patients did not have any clinically apparent heart disease. The clinical indications for an electrophysiological study included pre-syncope in five patients, paroxysmal atrial tachycardia in two patients, and paroxysmal atrial flutter in one patient. Group II consisted of eight patients (mean age 60 years, five males, three females) with abnormal sinus node function studies (SACT  $> 200$  msec and CRT  $> 395$  msec or

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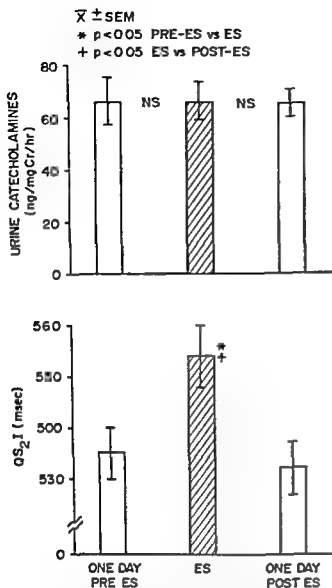


Fig 1 Urinary catecholamine excretion (top panel) and the QS<sub>2</sub>I (lower panel) determined on the day before the electrophysiological procedure (one day pre ES) on the day of the electrophysiological procedure (ES) and one day after the procedure (one day post ES)

SACT > 205 msec alone) Two patients had catheterization proven atherosclerotic coronary artery disease and other than primary conduction abnormalities the remaining six patients did not have clinically apparent heart disease The clinical indications for an electrophysiological study in this group included sick sinus syndrome in four patients syncope in two atrioventricular block in one and paroxysmal atrial tachycardia in one

**Procedure** Written informed consent was obtained from each patient prior to study The

adrenergic state of the patient was assessed by the determination of urinary catecholamine excretion<sup>11</sup> and by the measurement of the duration of electromechanical systole (QS<sub>2</sub>I)<sup>12</sup> Urine was collected beginning 2 hours prior to the electrophysiological study and ending 2 hours after the completion of the study The mean duration of urine collection during the procedure day was 6.2 hours Six hour urine collections were also obtained during the same time of day one day prior to and one day after the electrophysiological study Patients remained supine during each urine collection period The three urine samples of each patient were analyzed by Bioscience Laboratories (Van Nuys California) for total catecholamine content (epinephrine and norepinephrine) and creatinine The total catecholamine content of each sample was corrected for creatinine excretion and was then divided by the time period of collection the results are expressed as nanograms of catecholamine excreted per milligram creatinine per hour Systolic time intervals were measured using previously described techniques<sup>13</sup> immediately prior to the sinus node function studies in the catheterization laboratory Systolic time intervals were also obtained 2 hours after the beginning of the 6 hour urine collection one day prior to and one day after the electrophysiological study The duration of total electromechanical systole (QS<sub>2</sub>) was corrected for heart rate and expressed as total electromechanical systole index QS I

All medication was discontinued 48 hours prior to the electrophysiological study and no premedication was administered for the procedure The electrophysiological study was performed according to standard techniques All catheters were positioned with fluoroscopic assistance A bipolar catheter was placed in the high right atrium via a right antecubital vein venesection A bipolar recording catheter was passed into the esophagus to the level of the mid left atrium A six pole recording catheter was inserted into the right femoral vein (Seldinger technique) and was placed across the tricuspid valve<sup>14</sup> Intracardiac signals were amplified in a frequency range of 30 to 500 cycles/second and recordings were taken on an Electronics for Medicine DR 12 recorder at 50 and 100 mm/sec paper speed Atrial pacing and placement of atrial premature depolarizations (2× threshold) were accomplished by a Grass Instruments S88 stimulator and isolation

Table 1 Electrophysiological data obtained at the time of study (ES) and one day after the study (Post ES) in the subject population

Case No	Age/sex	SACT (msec)		CRT (msec)		EARP (msec.)		AA (msec)	
		ES	Post ES	ES	Post ES	ES	Post ES	ES	Post ES
Normal SA node function group (Group I)									
1	47 M	187	189	193	182	220	310	733	843
2	58 M	179	169	300	180	290	290	840	822
3	56 M	183	182	170	240	310	280	937	774
4	29 F	130	134	29	136	220	210	600	730
5	58 M	163	161	243	193	300	330	773	891
6	64 M	164	127	200	125	250	230	819	857
7	35 F	135	124	80	165	270	240	440	831
8	63 M	50	140	109	119	240	740	1184	949
$\bar{x}$	51	149	153	167	171	264	266	790	838
SD	13	45	25	68	47	38	43	214	68
SEM	3	16	9	31	15	13	15	76	24
Level of significance			NS		NS		NS		NS
Abnormal SA node function group (Group II)									
1	51 F	318	303	563	554	280	270	862	971
2	67 M	216	113	330	189	540	530	1192	1028
3	60 F	245	192	330	254	260	300	823	860
4	79 M	220	160	143	740	300	240	724	750
5	61 M	271	188	210	210	260	200	640	634
6	60 F	391	253	323	430	360	370	1376	753
$\bar{x}$	47 M	242	356	509	457	450	430	1067	860
8	60 M	472	760	369	345	395	435	1147	928
$\bar{x}$	60	290	279	348	332	348	361	973	849
SD	10	94	80	139	133	101	107	243	130
SEM	4	33	28	49	47	36	39	86	46
Level of significance			NS		NS		NS		NS

NS = not significant; SACT, CRT, EARP, and AA = see text.

unit. Systolic time intervals were performed with in 15 minutes after the placement of the catheters. Immediately after the completion of the systolic time intervals the sinus node function studies were started. Sinus node function was assessed by the determination of the sinoatrial conduction time (SACT) and sinoatrial recovery time. The SACT was obtained by the extrastimulus technique and equalled the AA interval minus the A-A interval where  $A_1$  = spontaneous atrial depolarization,  $A_2$  = premature atrial depolarization (extrastimulus) and  $A_3$  = the recovery atrial depolarization (sinus node origin). The SACT for each patient represents the mean of all determinations made at  $A_2/A_1$  of 0.40 to 0.60 (sinus reset zone). Overdrive suppression with rapid atrial pacing was used to obtain the sinoatrial recovery time. Atrial pacing at rates of 80 to 150 beats/minute (at 10 beats/minute incre-

ments) for greater than 30 seconds was used to suppress the sinus node. The immediate post pacing recovery cycle was used for the sinoatrial recovery time. The basic cycle length (AA interval) was subtracted from the sinoatrial recovery time and the difference was then expressed as the corrected recovery time (CRT). Each CRT value for each patient represents the mean of all the CRTs obtained during the sequence of atrial pacing; a minimum of six values was used. Normal values for our laboratory are SACT  $\leq 205$  msec and CRT  $\leq 395$  msec.

After the electrophysiological study, the esophageal and six pole catheters were removed. The patient was returned to his hospital room with the high right atrial catheter sutured in place. The position of this right atrial catheter was not changed from the beginning to the end of the study period. At the same time one day following

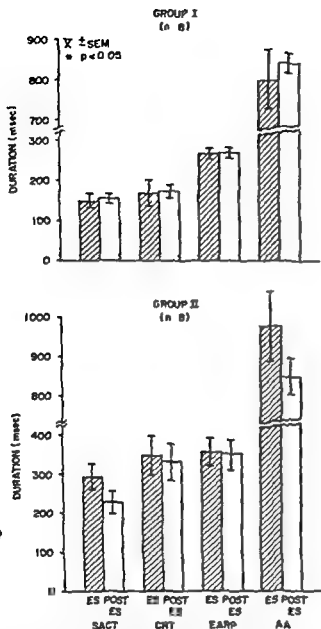


Fig 2 Electrophysiological data obtained on the day of the procedure (ES) and one day later (post ES) in patients with normal (Group I top panel) and in patients with abnormal (Group II lower panel) sinus node function studies AA CRT EARP and SACT = see text

the electrophysiological study, repeat sinus node function studies were performed in the patient's room. The SACT and CRT values were obtained immediately after the systolic time intervals and approximately two hours after the beginning of the six hour urine collection for that day.

The t test for paired data was used to analyze the statistical significance of changes between results obtained during the electrophysiological

study and that obtained one day after the study.

## Results

The adrenergic state of the patients as measured by urinary catecholamines and the QS<sub>1</sub>I during one day prior to and one day after the electrophysiological study are presented in Fig 1. The mean urine catecholamine excretion was not significantly different during the catheterization procedure than during comparable time periods the day before and the day after the procedure. The mean QS<sub>1</sub>I obtained during the electrophysiological study was significantly longer than the mean QS<sub>1</sub>I values obtained (in the patient's room) one day prior to and one day following the procedure.

The electrophysiological data are presented in Table I and are illustrated in Fig 2. The mean basic cycle length (AA interval) obtained in the hospital room on the day following the electrophysiological study did not differ significantly from that noted during the procedure.

The mean SACT of the normal SA node function group (Group I) did not change significantly from the procedure day to the day following the study (Fig 3A). Although the SACT of patient No 8 (Group I) increased by 90 msec, none of the patients in Group I demonstrated an increase of the SACT to the abnormal range the day following the procedure. The mean SACT of the patients with abnormal sinus node function (Group II) decreased slightly the day following the electrophysiological study. Although this change was not statistically significant, it is noteworthy that the SACT decreased in all patients of this group except in patient No 7. If patient No 7 is excluded, the mean SACT of Group II decreased significantly the day following the electrophysiological study. Patients No 2 and 8 decreased their SACT > 100 msec and patients No 2 through 5 normalized their SACT the day following the procedure.

The mean CRT did not change significantly for either group (Fig 3B). None of the patients with normal SA node function (Group I) prolonged CRT to the abnormal range on repeat study. One of the Group II patients with initial normal CRTs prolonged the CRT to the abnormal range the day after the procedure. The two patients with abnormally prolonged CRTs remained in the abnormal range on re study.

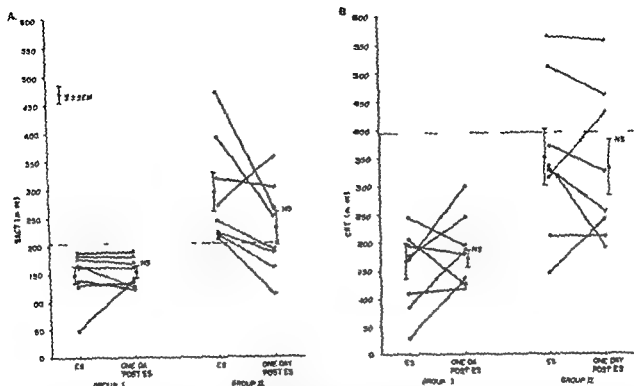


Fig 3 The SACT (panel A) and CRT (panel B) values obtained during the electrophysiological procedure (ES) and one day later (one day post ES) of individual patients with normal (Group I) and abnormal (Group II) SA node function studies. While the mean SACT of Group II did not change significantly, considerable variation in the SACT of individual patients over the two consecutive days was noted (panel A, right graph). While the CRT decreased in five patients of Group II, none of the values normalized on repeat study (panel B, right graph). One Group II patient prolonged his CRT into the abnormal range. NS = not significant.

The mean atrial effective refractory period of either group was not significantly different on the day following the electrophysiological study when compared to values obtained from the procedure. The mean atrial refractory period of Group II was significantly longer than that of Group I (t test for unpaired data); this may be secondary to the longer (but insignificant) basic cycle length of Group II.

#### Discussion

The increase in the  $QS_2I$  coupled with a lack of change in the urinary catecholamine excretion during the electrophysiological study suggest that the procedure did not elicit a hyperadrenergic response. The electrophysiological study performed in the catheterization laboratory appears more basal than the shorter and less involved procedure performed in the patient's hospital room. These results are at variance with the general impression that the electrophysiology laboratory is a continuously stressful situation

for the patient and with the results of Edmondson and associates and Turton and colleagues<sup>1</sup> showing that procedures specifically dental work and cardiac catheterization respectively increase plasma catecholamines. However, the plasma samples of these two studies were drawn at a time when the procedures were quite stressful and therefore may not be representative of the adrenergic state of the entire procedure. The short half life of circulating epinephrine and norepinephrine and the body's ability to increase these substances rapidly make the plasma catecholamine concentration merely a value reflecting the adrenergic state of a patient over a very short time period.<sup>11</sup> The urine catecholamines provide a physiological integration of plasma catecholamine concentrations over the period of time the urine sample is collected.<sup>1</sup> It is possible that the plasma catecholamine levels were high early in the electrophysiological study (during instillation of local anesthesia, venesection, etc.) and returned toward the basal state as the

patient became acclimated to the environment of dim lights and classical music. It is somewhat surprising that the QS<sub>1</sub>I was shorter in the hospital room than in the electrophysiology laboratory; this may be a reflection of the hospital activities of the day including venepunctures, physician rounds, and discussions.

The electrophysiological results of the patients with normal sinus node function (Group I) appears to be quite reproducible despite a probable mild increase in the adrenergic tone (decrease of the QS<sub>1</sub>I) on the day following the complete electrophysiological study. The mean basic cycle length (AA interval) of Group I patients was slightly shorter during the electrophysiological study primarily as a result of patient No. 7 who had sinus tachycardia during the procedure. If the results from patient No. 7 are deleted, the mean cycle length of Group I showed a tendency to decrease on the day following the procedure; this is similar to the basic cycle length changes of Group II and supports the hypothesis that the overall adrenergic tone for both groups was slightly greater the day following the procedure. A concomitant increase in the parasympathetic tone during the procedure cannot be definitely excluded. The SACT and CRT are both corrected for the spontaneous cycle length so that mild changes in the adrenergic tone would not be expected to result in a significant change in the corrected values. In general, it appears that when sinus node function studies obtained from the standard electrophysiological study are normal (Group I patients), the results are reproducible.

While the mean measurements of sinoatrial function in patients with sinus node dysfunction (Group II) did not change significantly, considerable variation in individual results occurred between the two consecutive study days. The basic cycle length decreased in five, the SACT shortened in seven, and the CRT decreased in five of the eight patients on the day following the electrophysiological study. Four patients normalized their SACT values the day after the procedure. Urine catecholamine and QS<sub>1</sub>I data do not show that these patients had greater adrenergic tone than the control group during the day following the procedure. It appears that in some patients the electrophysiological study induces an absolute or relative (reduced adrenergic tone) increase of parasympathetic tone; this would tend to lengthen the basic cycle length and

prolong the SACT and CRT. Somnolence, the quiet and dimly lit room placement and manipulation of catheters in veins (vasovagal) and a catheter in the esophagus (vago-vagal) might have increased the parasympathetic tone of some of the patients undergoing the complete electrophysiological study. However, since very few of the patients in the control group were noted to have a longer SACT, CRT, or cycle length during the standard electrophysiological study (compared to the day after the procedure), the sinoatrial region of some patients with abnormal SA node studies appears to respond more dramatically to an increase of parasympathetic tone. Using the general classification advanced by Jordan and colleagues<sup>11</sup> and by Thormann and associates<sup>12</sup>, the four patients of Group II that normalized their sinoatrial studies specifically the SACT (patients No. 2 through 5, Table I, Fig. 3) probably belong to the disturbances in autonomic regulation of sinus node function group, and the remaining patients in Group II have intrinsic sinus node disease.

It is unlikely that the parasympathetic effects on the sinoatrial function studies of some patients in Group II are secondary to a sympathetic induced parasympathetic tone mechanism.<sup>13</sup> Similar responses were not noted in the control group and the urine catecholamines were not elevated.

It is apparent that the electrophysiological study performed in a catheterization laboratory does not elicit a continuous hyperadrenergic response in most patients undergoing the procedure; in fact, the event appears to induce an absolute or relative increase in parasympathetic tone in some patients. Current measurements of sinoatrial function (SACT and CRT) as performed in the electrophysiology laboratory are reproducible in patients with normal baseline SA node function. In patients with abnormal SA node function studies, additional pharmacologic and/or physiologic maneuvers<sup>11,12</sup> should be performed in order to differentiate patients into those with intrinsic sinus node disease and those with abnormal autonomic regulation.

### Summary

Urinary catecholamine excretion remained unchanged and total electromechanical systole QS<sub>1</sub>I increased during the electrophysiological study of 16 patients (eight normals, eight with

sinus node dysfunction) when compared to values obtained the day before and the day after the study. The mean values of the sinus node function studies (sinuatrial conduction and recovery times) repeated the day after the procedure were not significantly different from those obtained during the electrophysiological study in both the normal patients and patients with sinus node dysfunction. Individual patients in the sinus node dysfunction group showed slight variation in the sinus node studies; four of these patients showed normalization of SA node function the day after the electrophysiological procedure.

These studies suggest that the electrophysiological procedure does not provoke a hyperadrenergic state. The sinus node function studies are reproducible in patients with normal baseline values. While the mean sinus node function results for the group with abnormal SA node function did not change significantly on repeat testing, some individual variation occurred; this variation is probably related to autonomic disturbances of SA node function.

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## Antihypertensive effect of BS 100-141,\* a new central acting antihypertensive agent

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N Amidino 2 (2,6 dichlorophenyl) acetamide hydrochloride (BS 100 141) is a phenylacetyl guanidine derivative which exerts an antihypertensive effect by stimulating central alpha adrenoreceptors.<sup>1,2</sup> This causes a reduction of sympathetic activity and depresses pressor circulatory reflexes.<sup>3</sup> At the same time it stimulates peripheral alpha adrenoreceptors and therefore orthostatic hypotension is prevented.<sup>1</sup> The mechanism of its hypotensive effect is therefore similar to clonidine, the sedative effect is however reported to be less. The purpose of the present trial was to determine the antihypertensive effect and dosage level in a population of Thai outpatients.

### Methods

Thirty six patients of both sexes were studied as outpatients at the University Hospital. Each patient in the study had been followed previously in the hypertensive clinic for several months or years and therefore knew the investigators and was familiar with the environment of the clinic. Written informed consent was obtained from each patient. Inclusion into the study required that the subject's age was 60 years or less and that his average diastolic blood pressure was 90 mm Hg or higher after at least one week of placebo. Only cooperative patients without malignant hypertension or other serious and incapacitating illnesses were studied. All had a

complete history and physical examination. Laboratory tests included hemoglobin, hematocrit, white cell count, sedimentation rate, urinalysis, chest x ray, electrocardiogram, BUN, creatinine, uric acid, sodium, potassium, chloride, alkaline phosphatase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and fasting blood sugar. In addition, rapid intravenous pyelograms and appropriate tests for pheochromocytoma were performed when indicated.

Following at least one week of placebo, the patients accepted into the study were assigned at random to two groups. Nineteen patients received BS 100 141 and seventeen received BS 100 141 placebo. The placebo tablets were indistinguishable from active tablets. Each tablet of BS 100-141 contained 2 mg of the drug. All medications were given orally. The initial dose was 4 mg of BS 100 141 per day or two tablets of placebo given in two divided doses. The patients were seen at intervals of one week for the next seven weeks. On subsequent visits at the interval of one week the physician added one tablet (2 mg) of BS 100 141 or placebo if the standing diastolic blood pressure was more than 90 mm Hg. An increment of 4 mg was given if the patient had already been taking 8 mg of BS 100 141 during the previous week. The maximum dose was 12 mg per day or two tablets of placebo three times a day. If the standing diastolic blood pressure was less than 90 mm Hg the dose was maintained. Non responders were removed from the study if the blood pressure did not fall following a week of 12 mg of BS 100 141 or six tablets of placebo. Blood pressure and heart rate were taken in the supine and standing position both immediately and 3 minutes after assuming this posture, and in the sitting position. The

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measurement was made with a standard sphygmomanometer following at least 15 minutes of rest. Cessation of sound was our criterion for diastolic blood pressure. All patients were told to omit the morning dose before coming for the examination. The patients were questioned concerning symptoms and were examined for adverse effects. If side effects interfered with the daily routine of the patient, the drug dosage was reduced to the level of the previous visit and either 60 mg of hydrochlorothiazide or 2.5 mg of bendroflumethiazide were added. The body weight was recorded at each visit. Laboratory tests were repeated at the end of the study.

## Results

**Patient characteristics** All patients were of Thai or Thai Chinese origin. There were 11 men and eight women in the BS 100 141 group as against seven men and 10 women in the placebo group. They all suffered from mild hypertension. The body weight of the BS 100-141 group was significantly higher (Table I) but sex, age, duration of hypertension and family history of hypertension were not statistically different. Analysis of the data at the end of the initial placebo period indicated that there were no significant differences in regard to supine standing and sitting blood pressure or pulse rate in supine and sitting. The standing pulse rate of the placebo group was higher compared to the BS 100-141 group. All patients in the BS 100-141 group completed the study whereas 12 patients in the placebo group were removed from the study as non responders. The number of patients and the daily dosage at the end of the treatment period are shown in Table II. 7 patients in the BS 100 141 group and one patient under placebo received a diuretic.

**Antihypertensive effects of BS 100 141** The effect of BS 100-141 and placebo on blood pressure and heart rate was compared statistically within the treatment groups by means of the Wilcoxon Rank Sum Test (level of significance  $2\alpha = 0.05$ ). The values of visit 2 (after treatment with placebo for 1 week) were compared with the values at visits 3 to 9.

As can be seen from Table III there was a significant decrease of the blood pressure under BS 100 141 from visits 3 to 9 in all postures. With placebo the comparison could only be made until visit 7. By visits 8 and 9 there was too much

Table I Age weight duration of illness

	Age (years)		Weight (kg)		Duration (years)	
	BS 100 141	Placebo	BS 100 141	Placebo	BS 100-141	Placebo
Mean	51	48	67	59	6.7	5.9
Standard deviation	7	10	11	11	5.7	5.5
Median	49	45	69	58	4.5	5.0
Range	39-69	30-60	51-86	45-83	1-20	0-19
n	19	17	19	17	18	15

Table II Dosage of BS 100 141 and placebo. Number of patients with number of tablets daily at the end of the treatment period in each group

	BS 100 141	Placebo
1 tablet daily	1 patient	0 patients
2 tablets daily	6 patients	0 patients
3 tablets daily	2 patients	1 patient
4 tablets daily	4 patients	0 patients
5 tablets daily	4 patients	16 patients

missing data because of dropouts for ineffectiveness. With few exceptions no significant change in blood pressure was observed under placebo. The heart rate (Table IV) decreased significantly in the actively treated group in the supine and sitting postures whereas in the standing posture the differences were not statistically significant. In the group under placebo treatment no statistical evaluation was indicated since pulse rate did not change.

The comparison between the two groups elicited the following data. The homogeneity of the two groups regarding the baseline blood pressure and heart rate was tested by means of the U test. With the exception of the heart rate in the standing posture no differences were observed between the two groups.

The differences between the values obtained at visits 3 to 7 and the baseline value (visit 2) in the BS 100 141 group have been compared with the corresponding differences in the placebo group using the U test according to Mann-Whitney and Wilcoxon. The values of visits 8 and 9 of the placebo group could not be evaluated for reasons already mentioned. This comparison showed

Table III Blood pressure (mean values  $\pm$  standard deviation)

Visit	Supine				Sitting				Standing			
	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.
1	154 $\pm$ 17	97 $\pm$ 8	140 $\pm$ 20	101 $\pm$ 10	147 $\pm$ 19	104 $\pm$ 17	143 $\pm$ 26	100 $\pm$ 27	150 $\pm$ 20	105 $\pm$ 11	148 $\pm$ 27	102 $\pm$ 14
	Placebo				Placebo				Placebo			
2	160 $\pm$ 18	102 $\pm$ 7	160 $\pm$ 19	100 $\pm$ 7	149 $\pm$ 20	100 $\pm$ 7	154 $\pm$ 20	100 $\pm$ 8	159 $\pm$ 17	110 $\pm$ 7	161 $\pm$ 22	111 $\pm$ 10
	Placebo		BS 100-141		Placebo		BS 100-141		Placebo		BS 100-141	
3	158 $\pm$ 15	100 $\pm$ 7	145 $\pm$ 15	97 $\pm$ 10	140 $\pm$ 15	99 $\pm$ 7	130 $\pm$ 20	91 $\pm$ 12	153 $\pm$ 16	106 $\pm$ 10	131 $\pm$ 20	94 $\pm$ 14
	n.s.	n.s.			n.s.				n.s.			
4	154 $\pm$ 19	99 $\pm$ 8	140 $\pm$ 20	97 $\pm$ 11	140 $\pm$ 27	100 $\pm$ 10	133 $\pm$ 21	90 $\pm$ 11	153 $\pm$ 21	104 $\pm$ 9	132 $\pm$ 22	90 $\pm$ 11
	n.s.				n.s.				n.s.			
5	161 $\pm$ 20	103 $\pm$ 9	143 $\pm$ 20	92 $\pm$ 10	148 $\pm$ 18	106 $\pm$ 28	130 $\pm$ 21	91 $\pm$ 11	160 $\pm$ 21	107 $\pm$ 11	134 $\pm$ 22	98 $\pm$ 13
	n.s.	n.s.			n.s.	n.s.			n.s.	n.s.		
6	168 $\pm$ 20	104 $\pm$ 8	140 $\pm$ 20	97 $\pm$ 9	160 $\pm$ 17	111 $\pm$ 18	133 $\pm$ 15	93 $\pm$ 9	161 $\pm$ 21	108 $\pm$ 10	133 $\pm$ 19	97 $\pm$ 11
	n.s.	n.s.			n.s.	n.s.			n.s.	n.s.		
7	163 $\pm$ 15	104 $\pm$ 7	142 $\pm$ 19	93 $\pm$ 10	160 $\pm$ 19	104 $\pm$ 10	128 $\pm$ 20	88 $\pm$ 9	159 $\pm$ 19	108 $\pm$ 12	128 $\pm$ 19	90 $\pm$ 10
	n.s.	n.s.			n.s.	n.s.			n.s.	n.s.		
8	168 $\pm$ 10	103 $\pm$ 5	146 $\pm$ 27	93 $\pm$ 13	164 $\pm$ 16	99 $\pm$ 10	130 $\pm$ 26	90 $\pm$ 14	160 $\pm$ 10	108 $\pm$ 8	129 $\pm$ 23	92 $\pm$ 10
9	158 $\pm$ 21	104 $\pm$ 5	142 $\pm$ 19	94 $\pm$ 9	160 $\pm$ 14	106 $\pm$ 7	129 $\pm$ 16	83 $\pm$ 10	152 $\pm$ 14	112 $\pm$ 10	129 $\pm$ 15	96 $\pm$ 8

 $p < 0.05$  $p < 0.01$  $p < 0.001$ Table IV Heart rate (mean values  $\pm$  standard deviation)

Visit	Supine		Sitting		Standing	
1	69 $\pm$ 7	72 $\pm$ 8	73 $\pm$ 10	74 $\pm$ 10	77 $\pm$ 9	76 $\pm$ 8
	Placebo		Placebo		Placebo	
2	73 $\pm$ 8	71 $\pm$ 9	76 $\pm$ 8	73 $\pm$ 9	82 $\pm$ 7	77 $\pm$ 8
	Placebo		BS 100-141		Placebo	
3	73 $\pm$ 7	60 $\pm$ 8	77 $\pm$ 7	70 $\pm$ 8	78 $\pm$ 5	73 $\pm$ 10
	n.s.					n.s.
4	70 $\pm$ 7	63 $\pm$ 9	75 $\pm$ 8	66 $\pm$ 10	80 $\pm$ 7	72 $\pm$ 10
	n.s.					n.s.
5	73 $\pm$ 7	60 $\pm$ 11	77 $\pm$ 9	68 $\pm$ 11	77 $\pm$ 7	75 $\pm$ 11
	n.s.					n.s.
6	72 $\pm$ 7	61 $\pm$ 8	70 $\pm$ 7	69 $\pm$ 12	80 $\pm$ 10	71 $\pm$ 10
	n.s.					n.s.
7	74 $\pm$ 7	60 $\pm$ 9	77 $\pm$ 9	68 $\pm$ 9	83 $\pm$ 11	72 $\pm$ 10
	n.s.			n.s.		n.s.
8	78 $\pm$ 7	67 $\pm$ 9	76 $\pm$ 5	69 $\pm$ 11	82 $\pm$ 8	74 $\pm$ 11
	n.s.			n.s.		n.s.
9	83 $\pm$ 10	60 $\pm$ 8	82 $\pm$ 12	66 $\pm$ 7	68 $\pm$ 7	69 $\pm$ 13
	n.s.			n.s.		n.s.

 $p < 0.05$

**Table V** Number and kind of side effects in each treatment group

	BS 100 141	Placebo
Dry mouth	17 patients	2 patients
Insomnia	7 patients	1 patient
Fatigue	6 patients	1 patient
Dizziness	4 patients	1 patient
Palpitations	2 patients	1 patient
Anxiety	2 patients	0 patients
Anorexia	1 patient	0 patients
Orthostat hypotension	1 patient	0 patients
Constipation	1 patient	0 patients
Headache	0 patients	1 patient
Total side effects/Number of patients	43/18	7/3

significant differences between the average blood pressure values in all postures and in heart rate in the sitting and supine postures in favor of BS 100-141.

#### Dosage of BS 100 141

The dosage of BS 100-141 at the end of the study can be seen in Table II. Fifteen patients received 2 to 8 mg/day, eight of whom were on 2 mg twice a day. In the four patients in whom the dosage was increased from 8 to 12 mg/day for the last 2 or 3 treatment weeks, no additional benefit was obtained.

**Side effects (Table V).** The most important side effects related to BS 100 141 were dry mouth, insomnia, fatigue and dizziness. In general, these side effects were of mild nature and did not interfere with the everyday activity of the patients. A transitory reduction of the dosage had to be performed six times because of dry mouth, fatigue, dizziness or insomnia. In no patient did the treatment have to be interrupted because of side effects. Neither orthostatic hypotension nor edema were observed in this group of patients.

#### Estimation of drug effectiveness

A scoring of drug efficacy was made at each visit by comparing the reduction of blood pressure to that obtained in the previous visit. Table VI summarizes the results following one week of 4 mg/day of BS 100 141.

The result demonstrates a favorable effect of BS 100 141 with 14 patients in the excellent and good groups is compared with two cases in the placebo group.

**Table VI** Physician's estimation of efficacy

Efficacy after 1 week of treatment	BS 100-141	Placebo
Excellent	10 patients	1 patient
Good	4 patients	1 patient
Fair	1 patient	1 patient
Slight	1 patient	3 patients
None	3 patients	10 patients
Worse	0 patients	1 patient
Binomial probability	2 p < 0.001	n.s.

(Excellent + good + fair vs. slight + worse),  $\chi^2$ -statistic (between groups)  $\chi^2 = 14.51$ ,  $7p < 0.001$ .

Excellent = reduction of standing diastolic blood pressure of 90 mm. Hg or below. Good = reduction of 50% or more of standing blood pressure that is above 90 mm. Hg. Fair = reduction of less than 50% of standing blood pressure that is above 90 mm. Hg. Slight = minimal reduction of blood pressure.

#### Laboratory investigations

Serum potassium, sodium, chloride, uric acid, blood glucose, blood urea, nitrogen, SGOT and SGPT and alkaline phosphatase obtained during control and at the end of the treatment remained unchanged. Blood glucose and uric acid increased significantly during BS 100-141 treatment. Hyperuricemia occurred in all seven patients on BS 100 141 to whom a diuretic had been given. Fasting blood sugar increased in all patients except three. Two patients were known to be diabetic; a diuretic was added in seven patients. The level of glucose did not rise above the upper limits of normal except in two patients, one of whom was a diabetic. Sedative effects did not occur.

#### Hypertensive rebound

Following the completion of the study, the treatment with BS 100 141 was discontinued and various antihypertensive agents were substituted which had previously proved effective in the individual patients. The patients were given an appointment for a follow up visit within two weeks.

With clonidine it is known that the occurrence of so called rebound hypertension is frequent. This term is not exactly characterized but in general it is assumed that rebound hypertension is present if the blood pressure rises considerably above the values measured before active treatment (diastolic 130 mm. Hg or more) and if at the same time distinct signs of sympathetic over-

Table VII

Case no	Age	Sex	Final dosage of BS 100 141 mg /day	Drug taken after BS 100 141	Blood pressure before BS 100 141 treatment	Blood pressure under BS 100 141	Blood pressure 2-4 days after interruption
1	61	male	8	Hydrochlorothiazide	Supine 170/110 Standing 180/110 Sitting 150/104	150/100 148/100 138/90	180/124 156/120 154/132
8	49	male	8	Iso Trraupin	Supine 170/120 Standing 180/130 Sitting 170/130	140/100 140/108 140/102	166/124 122/126 —
14	49	male	6 + Pluryl K	Prazosin Pluryl K	Supine 140/110 Standing 140/110 Sitting 124/100	112/94 114/96 116/90	114/110 160/132 166/120
16	61	female	8	Iso Trraupin	Supine 160/100 Standing 160/100 Sitting 160/100	122/78 130/84 124/76	170/120 — 170/124

charge are observed—mainly tachycardia abdominal cramps pilar erection anxiety etc

Four patients in our series showed a rise in blood pressure in the days following discontinuation of the treatment (see Table VII). The symptomatology is described below. Whether a classical rebound phenomenon occurred in these cases or whether there was merely a reappearance of the previously existing hypertension is open to discussion. The cases were Nos 1 6 14 and 16.

**Case No 1** A 61 year old grocer had been treated for his hypertension for one year. Control blood pressure following one week of placebo was 70/110 182/114 and 158/104 under BS 100 141. It decreased to 150/100 140/100 and 138/90 mm Hg in the supine standing and sitting posture respectively. The dosage of BS 100 141 was 8 mg daily. Except for dry mouth and dizziness of mild degree during the drug trial his course was uneventful. After the trial 50 mg hydrochlorothiazide per day was substituted for BS 100 141. Two days following cessation of BS 100 141 severe headache developed requiring an analgesic. He became unwell and had palpitations. The symptoms lasted to the time of examination ten days later. His blood pressure then was 180/124 156/120 154/132 mm Hg in the supine standing and sitting posture respectively. Alphamethyl dopa was added and the patient was normotensive when reexamined a week later.

**Case No 6** A 49 year old colonel was a known hypertensive for 10 years. He had not been taking any antihypertensive drugs for the previous two months before entering the BS 100 141 drug trial. His blood pressure following a week of placebo

was 170/120 182/134 and 170/132 mm Hg in the supine standing, and in the sitting posture respectively. After taking BS 100 141 8 mg daily the blood pressure was 140/100 140/108 and 140/102 mm Hg respectively. The only symptom during the drug trial was insomnia which occurred during the last four weeks. At the end of the trial 1 tablet of Iso Trraupin twice daily was substituted for BS 100 141. The patient developed headache palpitations restlessness and insomnia two days following cessation of BS 100 141. His blood pressure was elevated to 166/124 and 172/126 mm Hg in the supine and standing positions.

**Case No 14** A 49 year old male school teacher was a known hypertensive for over 20 years. He complained of fatigue while taking 8 mg BS 100 141 so the dose was reduced to 6 mg and 1 tablet of Pluryl K was added. His blood pressure decreased from a control level of 140/110 140/110 and 130/110 mm Hg to 112/94 114/94 and 116/90 mm Hg in the supine standing and sitting positions respectively. At the end of the treatment prazosin 4 mg and 50 mg of hydrochlorothiazide daily were substituted for BS 100 141. He was seen four days later with palpitations and chest discomfort. Blood pressure was elevated to 154/110 160/132 and 166/120 mm Hg in the supine standing and sitting positions respectively. The medications were changed to propranolol 80 mg alphamethyl dopa 750 mg and hydrochlorothiazide 50 mg. Blood pressure was normal at the following examination a week later.

**Case No 16** A 61 year old housewife was

known to be hypertensive for the past 11 years. She was asymptomatic taking 8 mg of BS 100 141 and her control blood pressure which had been 160/102, 162/104 and 150/100 mm Hg in the supine, standing and sitting position became normal. Iso Trirapin\* was given following the cessation of BS 100 141. She was seen 14 days later when she complained of fatigue and giddiness. Her blood pressure had risen up to 170/120 mm Hg in the supine and 170/124 mm Hg in the sitting position.

## Discussion

BS 100 141, a new antihypertensive guanidine derivative, has been compared with placebo in a double blind trial in 36 patients (19 active, 17 placebo). The average blood pressure of the patients under active treatment was significantly lowered from the first week of the trial onwards, whereas the patients under placebo showed practically no effect. In 14 of the 19 patients under treatment with BS 100 141, the diastolic blood pressure fell to 90 mm Hg or less already in the first week. The dose range of BS 100 141 was between 4 and 8 mg daily. An increase of the dosage from 8 to 12 mg per day which was tried in four patients did not improve the therapeutic results. Orthostatic hypotension was not observed; thus may be due to the peripheral alpha stimulating effect of the drug.<sup>1</sup> Although there was a significant reduction of the pulse rate in the sitting position, it was never 60 per minute in either position. Our findings are in agreement with those of other investigators.

BS 100 141 was generally well tolerated and no serious side effect was recorded during the entire period of treatment. There were secondary side effects, however, and in one case the dose had to be reduced, but the treatment was never interrupted because of untoward reactions. The most frequently occurring side effects were:

dry mouth	17 patients
insomnia	7 patients
fatigue	6 patients
dizziness	4 patients

Three patients under placebo reported seven side effects of the same nature.

The only biochemical change of potential importance was a tendency to an increase in

blood glucose. Close observation of the blood sugar is therefore indicated in patients with preexisting diabetes mellitus.

After a sudden interruption of the treatment in four of 19 patients, the blood pressures rose to pretreatment values or slightly higher without any serious consequences. Discontinuation of the treatment, however, should be done gradually.

## Summary

A double blind comparison between BS 100 141 and placebo in 36 hypertensive patients of Thai or Thai-Chinese origin revealed that the preparation lowers the elevated blood pressure within the first week of treatment in most patients. The drug was relatively well tolerated and caused mild side effects only. After a sudden discontinuation of the drug, the blood pressure in four of the 19 patients increased within a few days to pretreatment values or slightly above. The occurrence of rebound hypertension cannot be excluded. Interruption of treatment therefore should be made gradually.

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\*Iso-Trirapin is manufactured by Boehringer GmbH, Mannheim, W. Germany.

# The effect of hemodilution with stroma-free hemoglobin and dextran on collateral perfusion of ischemic myocardium in the dog

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The area of ischemia following the sudden occlusion of a major coronary artery is composed of a core ischemic area and a surrounding marginal zone. In the former blood supply is minimal and unless flow is restored rapidly irreversible ischemic damage follows. In the marginal zone however potentially adequate collateral blood flow may exist and appropriate interventions designed to alter the balance of oxygen supply and demand may ensure survival of this zone.<sup>1</sup> Salvage of this marginal zone to minimize the mass of subsequently infarcting myocardium has great prognostic significance both in relation to complications in acute phase and in relation to the longer term effects of a subsequent ischemic event.<sup>2</sup> Consequently the aim of most therapeutic interventions in the acute phase is to salvage the marginal zone.

Perfusion of the marginal zone through collateral vessels is limited by the available pressure gradient and by local vascular resistance. Since it is probable that collateral vessels are maximally dilated flow under the prevailing pressure gradient is limited by blood viscosity. Since blood viscosity is primarily a function of the hematocrit<sup>3</sup> and since blood viscosity appears to increase early in myocardial infarction in man and in the dog it would be anticipated that hemodilution the reduction of the hematocrit and there-

by of blood viscosity may be beneficial and may improve perfusion of the marginal zone through the available collateral channels. The available experimental evidence indicates that following hemodilution with dextran collateral flow to the marginal zone is in fact increased<sup>4-11</sup> and that the severity of ischemic injury is not aggravated<sup>1</sup> or even ameliorated.<sup>1</sup> The most important disadvantage of hemodilution however is the proportional dilution of oxygen capacity and content. Thus while hemodilution may improve flow it is not clear whether this can offset the attendant reduction in oxygen content. In fact Kleinman and colleagues<sup>12</sup> demonstrated an impairment of oxygen supply especially to the subendocardium by the collaterals during hemodilution with dextran.

It has been demonstrated that a solution of stroma free hemoglobin (SFH) can be administered without the complications seen with massive in vivo hemolysis.<sup>1</sup> Hemodilution with SFH produces a reduction in blood viscosity comparable to that produced by similar dilution with dextran but permits the transport of substantially more oxygen in the plasma phase. It was also shown that in the normal heart hemodilution with SFH was followed by marked increase in coronary blood flow favouring the subendocardial layers. Furthermore the same procedure appears to prevent the rise in blood viscosity seen in the early phase of myocardial ischemia in the dog. These findings suggest a further possibility in the salvage of ischemic myocardium that of achieving the viscosity reducing effects of hemodilution with an agent capable of transporting significant amounts of oxygen. Accordingly the present experiments

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were undertaken to assess the short term effectiveness of hemodilution with SFH in improving oxygen supply to the marginal zone of ischemic myocardium following an acute coronary occlusion

### Methods

The experiments were performed on 26 male mongrel dogs (weight range 13.6 to 26.8 kilograms) under Nembutal (30 mg/kg) anesthesia. The protocol consisted of the following: the surgical preparation (see below) was followed by a 30 minute period to allow the attainment of a stable cardiovascular state. The experiment proper was begun with an initial control period when measurements were obtained. This was followed immediately by induction of myocardial ischemia when the previously placed snare was tightened on the left anterior descending coronary artery. During the next hour measurements were made at intervals. At the conclusion of the measurements at the one hour post occlusion period a rapid exchange transfusion was performed: blood was removed by the femoral artery (30 to 35 ml/kg) and an equivalent volume was reinfused into the femoral vein. In nine dogs SFH was infused in another nine dogs their shed blood was returned and in a further six dogs 6% dextran 70 was given in the same manner. This divergence in the protocol resulted in three groups. Group I comprised the test group of animals subjected to the exchange with SFH; those in Group II served as the control subjected to a sham exchange with their own blood and Group III comprised a further control series subjected to hemodilution but without the ability to transport significant oxygen in the plasma phase. During the subsequent two hours measurements were made at intervals in all three groups which were treated in an identical manner.

The surgical procedure was also identical in all animals. Catheters were placed in both femoral arteries and veins (one of these was advanced to the pulmonary artery). The chest was opened on both sides in the fifth intercostal space care being taken to effect hemostasis with electrocautery. On the left side a short polyethylene catheter was placed in the left atrium and a catheter tip pressure transducer (Millar Instruments Micro-Tip PC 350A) was inserted in the left ventricular cavity through the apex. A loose ligature was placed about the left anterior descending coronary

**Table 1** The composition of the SFH solution used in the experiments in Group I

Total hemoglobin	8.1 g/dl
Methemoglobin	5% of total pigment
Sodium	172 mEq/L
Calcium	2.5 mEq/L
Chloride	93 mEq/L
Calcium	5.5 mEq/L
Magnesium	1.7 mEq/L
pH	7.17
O <sub>2</sub> capacity	10.2 ml/dl
Total osmolality	278 mOsm/kg
Bacterial growth	—

ary artery beyond its first septal branch. On the right side a catheter was inserted in the coronary sinus and fixed so that its tip lay 2 cm from the valve of the coronary sinus. This placed it downstream to all important tributaries.

During the whole subsequent experiment the animals were ventilated through a cuffed endotracheal tube with room air using a Harvard respiratory pump with an expiratory resistance of 4 cm H<sub>2</sub>O. The rate and volume of ventilation were adjusted at the beginning of each experiment to maintain pO<sub>2</sub> and pCO<sub>2</sub> in arterial blood within the physiological range.

The following hemodynamic variables were recorded periodically on an Electronics for Medicine VR 6 Simultaneous recorder: phasic arterial blood pressure, phasic left ventricular pressure and its derivative (dp/dt), Lead II of the surface ECG. The cardiac output was determined by dye dilution using indocyanine green dye and a Waters densitometer (D400)-cuvette (AC302) system. Calibrations were performed with the dogs own blood with and without SFH and dextran as appropriate. Calculations were made on a Wang 600 programmable calculator.

Blood samples were drawn anaerobically from the arterial and coronary sinus catheters at intervals. In these samples pO<sub>2</sub>, pCO<sub>2</sub>, and pH were determined with an IL 113 Blood Gas Analyzer (Instrumentation Laboratories) at 37° C. The measured values were corrected using standard nomograms. The O<sub>2</sub> content was also determined in these samples using a LEX O CON TL (Lexington Instruments) oxygen analyzer. Arterial blood samples were used for the determination of hemoglobin concentration in whole blood and in the plasma phase (by the cyanmethemoglobin



**Table II** Blood parameters (mean  $\pm$  SEM) measured in arterial blood in Group I before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	Post occlusion		Post SFH hemodilution	
	Control 0'	30'	60'	30'	60'
Arterial blood					
pO	84.1 $\pm$ 6.7	76.0 $\pm$ 8.1	77.7 $\pm$ 7.1	80.0 $\pm$ 9.9	78.3 $\pm$ 8.5
pCO	32.2 $\pm$ 1.0	34.4 $\pm$ 1.0	35.3 $\pm$ 1.4	37.7 $\pm$ 1.8	39.7 $\pm$ 2.6 †
pH	7.37 $\pm$ .003	7.35 $\pm$ .04	7.35 $\pm$ .03	7.33 $\pm$ .02	7.31 $\pm$ .03 †
O content	20.2 $\pm$ 0.6	20.0 $\pm$ 0.5	20.4 $\pm$ 0.4	14.6 $\pm$ 0.6 †	14.7 $\pm$ 0.8 †
O saturation	87.1 $\pm$ 6.5	89.0 $\pm$ 6.2	88.2 $\pm$ 7.0	79.0 $\pm$ 7.7	86.4 $\pm$ 8.5
[HGB] whole blood	17.1 $\pm$ 1.0	16.5 $\pm$ 1.0	16.4 $\pm$ 0.7	12.0 $\pm$ 0.8 †	12.2 $\pm$ 1.3 †
plasma	0.2 $\pm$ 0.2	0.3 $\pm$ 0.1	0.3 $\pm$ 0.1	3.7 $\pm$ 1.9 †	3.3 $\pm$ 1.8 †
Hct	49 $\pm$ 3	49 $\pm$ 2	50 $\pm$ 2	28 $\pm$ 2 †	27 $\pm$ 1 †
O capacity					
whole blood	23.1 $\pm$ 0.8	22.4 $\pm$ 1.2	23.3 $\pm$ 0.9	18.5 $\pm$ 1.2 †	17.0 $\pm$ 1.1 †
plasma	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	4.9 $\pm$ 0.2 †	4.6 $\pm$ 0.2 †

Indicates statistically significant change ( $p < .05$ ) by paired t test from the pre-occlusion control value

†Indicates statistically significant change ( $p < .05$ ) by paired t test from the 60 minute post occlusion value

**Table III** Blood parameters (mean  $\pm$  SEM) measured in arterial blood in Group II before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	Post-occlusion		Post-exchange	
	Control 0'	30'	60'	30'	60'
Arterial blood					
pO	83.2 $\pm$ 5.7	78.0 $\pm$ 9.1	80.2 $\pm$ 8.1	81.6 $\pm$ 7.9	80.6 $\pm$ 6.4
pCO	34.2 $\pm$ 1.6	35.7 $\pm$ 1.5	35.9 $\pm$ 1.7	36.1 $\pm$ 1.3	35.9 $\pm$ 1.7
pH	7.35 $\pm$ .00	7.34 $\pm$ .03	7.34 $\pm$ .04	7.33 $\pm$ .06	7.34 $\pm$ .00
O content	19.6 $\pm$ 0.9	19.1 $\pm$ 0.7	20.1 $\pm$ 0.5	19.5 $\pm$ 0.8	19.0 $\pm$ 0.9
O saturation	90.0 $\pm$ 7.1	85.7 $\pm$ 8.1	91.1 $\pm$ 7.6	90.6 $\pm$ 6.3	88.2 $\pm$ 6.7
[HGB] whole blood	16.4 $\pm$ 1.1	16.7 $\pm$ 1.3	16.6 $\pm$ 1.1	16.1 $\pm$ 1.3	15.9 $\pm$ 1.4
plasma	0.2 $\pm$ 0.2	0.2 $\pm$ 0.1	0.3 $\pm$ 0.1	0.3 $\pm$ 0.1	0.4 $\pm$ 0.1
Hct	48 $\pm$ 3	48 $\pm$ 3	48 $\pm$ 2	48 $\pm$ 2	47 $\pm$ 1
O capacity					
whole blood	21.8 $\pm$ 1.1	22.2 $\pm$ 1.3	22.1 $\pm$ 1.1	21.5 $\pm$ 1.6	21.3 $\pm$ 1.5
plasma	0.5 $\pm$ 0.1	0.4 $\pm$ 0.2	0.4 $\pm$ 0.2	0.6 $\pm$ 0.1	0.7 $\pm$ 0.2

method) the hematocrit (by capillary method) and the oxygen capacity of whole blood and of the separated plasma phase. Separate arterial and coronary sinus samples were drawn into chilled syringes for the determination of creatine phosphokinase activity.

Myocardial blood flow and its distribution were estimated from the trapping of radionuclide labelled microspheres ( $15 \pm 3 \mu\text{m}$ ) ( $^{59}\text{Fe}$ ). These were prepared and injected into the left atrium according to procedures developed by others. Microspheres labelled with  $^{125}\text{I}$  were injected in the pre occlusion control period; those labelled with  $^{86}\text{Sr}$  were injected one hour after the

occlusion and those labelled with  $^{86}\text{Sr}$  were injected one hour after the exchange transfusion. Absolute and relative blood flow calculations were made using arterial reference samples drawn during and after the injections. At the conclusion of the experiment the heart was removed; separate epicardial and endocardial samples were taken from the visibly ischemic area from the marginal zone and from the normal regions. These tissue samples were digested in 4N KOH for 48 hours. Radioactivity was determined in the digested samples in a Packard two channel gamma spectrometer (3002) using three passes at settings previously deter-

Table IV Blood parameters (mean  $\pm$  SEM) measured in arterial blood in Group III before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	Post-occlusion		Post dextran hemodilution	
	Control 0'	30'	60'	30'	60'
Arterial blood					
pO <sub>2</sub>	87.1 $\pm$ 5.6	84.1 $\pm$ 6.7	83.2 $\pm$ 5.9	84.1 $\pm$ 6.2	80.0 $\pm$ 5.9
pCO <sub>2</sub>	34.1 $\pm$ 1.6	35.2 $\pm$ 1.1	35.4 $\pm$ 1.3	35.1 $\pm$ 1.1	35.2 $\pm$ 1.4
pH	7.36 $\pm$ 0.04	7.35 $\pm$ 0.06	7.34 $\pm$ 0.06	7.32 $\pm$ 0.06	7.32 $\pm$ 0.04
O <sub>2</sub> content	19.8 $\pm$ 0.9	19.1 $\pm$ 0.8	18.8 $\pm$ 1.2	10.9 $\pm$ 1.1	9.8 $\pm$ 0.8
O <sub>2</sub> saturation	89.7 $\pm$ 5.8	88.0 $\pm$ 6.1	85.3 $\pm$ 5.8	91.8 $\pm$ 6.7	91.9 $\pm$ 6.1
[HGB] whole blood	16.5 $\pm$ 1.1	16.3 $\pm$ 1.3	16.4 $\pm$ 1.2	8.9 $\pm$ 1.6	8.0 $\pm$ 1.5
plasma	0.2 $\pm$ 0.1	0.2 $\pm$ 0.2	0.3 $\pm$ 0.1	0.3 $\pm$ 0.2	0.4 $\pm$ 0.2
Hct	48 $\pm$ 4	49 $\pm$ 7	49 $\pm$ 2	26 $\pm$ 3	24 $\pm$ 3
O <sub>2</sub> capacity whole blood	21.9 $\pm$ 1.7	21.7 $\pm$ 1.5	2.0 $\pm$ 1.3	11.9 $\pm$ 1.7	10.7 $\pm$ 1.3
plasma	0.4 $\pm$ 0.1	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1

Indicates statistically significant change ( $p < 0.05$ ) by paired *t* test from the 60-minute post-occlusion value

mined to minimize spectral overlap. Calculations of blood flow were made using a program developed for this purpose on a Wang 600 calculator.

The stroma free hemoglobin (SFH) solution used in these experiments was prepared using sterile techniques in a single batch from out of date human packed erythrocytes by the method of Rabner and co-workers.<sup>2</sup> A separate batch prepared previously by the same method was tested in rabbits and dogs; it was free of pyrogens and only a transient ( $< 2$  min) hypotensive reaction was occasionally seen when administered rapidly in an exchange transfusion (40 ml/Kg). The electrolyte composition of the SFH reflected that of hemodialysis fluid (Formula Q Anachemia Ltd) used in dialysing it. The composition is listed in Table I. Dextran was prepared from powder form as a 6% solution in Ringers.

In a preliminary series of experiments the ischemic region following occlusion of the LAD artery was delineated in seven dogs. This was done by comparison of the stained myocardium after postmortem injection of Toluidine Blue in the aortic root with the distribution of microspheres. The visible ischemic area had a mean flow of  $21 \pm 4\%$  of the preocclusion value while the marginal zone was  $7 \pm 2$  mm wide on the epicardial surface with a mean flow of  $52 \pm 6\%$  of the preocclusion value. The unaffected myocardium received  $127 \pm 8\%$  of the preocclusion flow.

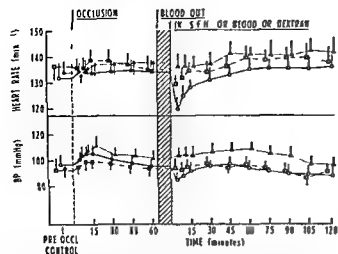
Statistical analysis was performed on a Wang 600 programmable calculator utilizing paired *t*

tests to detect significant changes within groups and Duncan's multiple range tests to detect differences between groups.

## Results

**1 Pre occlusion control period** The dogs comprising the three groups were not different in the preocclusion control period with respect to arterial and coronary sinus blood gas parameters (Tables II to IV and Fig 3) hemodynamic variables (Figs 1 and 2) and myocardial blood flow (Table V). Because of the extensive surgical damage to thoracic muscles CPH activity found in peripheral (arterial) blood was already excessive (range 280 to 370 mU/ml); it was for this reason that we elected to measure CPH difference across the heart and subsequently to calculate CPH output using the measured myocardial blood flow as a semiquantitative index of ischemic myocardial damage resulting in leakage of the enzyme.

**2 Effects of coronary occlusion** Occlusion of the LAD artery was followed by transient dysrhythmias in only four dogs of these three dysrhythmias subsided spontaneously within five minutes. The one experiment with persistent dysrhythmia (runs of VPBs and bigeminy) was discarded. All other animals survived until the experiment was terminated three hours or later following the occlusion without any drugs save the supplements of anesthetic as required. Qualitatively and quantitatively the changes during the 60 minute period following the occlusion were

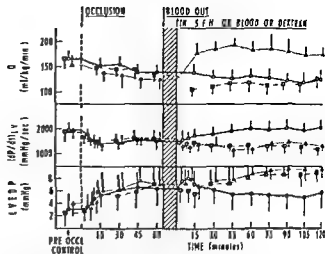


**Fig 1** Time course of systemic hemodynamic changes (heart rate and mean arterial blood pressure [mean  $\pm$  SEM]) following coronary occlusion and following the exchange transfusions. Circles indicate Group I hemodiluted with SFH solution; squares indicate Group II reinfused with whole blood; triangles indicate Group III hemodiluted with dextran 70. For details see text.

essentially similar in the three groups. Arterial blood pO<sub>2</sub> fell in all three groups but only in Group I did the fall attain statistical significance by paired t test ( $p < 0.05$ ); similar though smaller changes in the opposite direction were observed in arterial blood pCO<sub>2</sub>.

In terms of hemodynamic variables similar trends were evident in all three groups (Figs 1 and 2) while heart rate remained constant; mean arterial pressure tended to rise; Group III maintained the greatest extent. Cardiac output and stroke volume tended to fall while left ventricular end diastolic pressure rose. None of these changes was statistically significant. A consistent decrease was evident in L V dP/dt of approximately 25%; this decrement was significant in all three groups at the 15 minute period. All three groups exhibited a fall in coronary sinus pO<sub>2</sub> and oxygen saturation (Fig 3) of approximately 3 to 4 mm Hg and 5 to 6% respectively. The levels attained were approximately equal at the 30 and 60 minute post occlusion periods. At the latter time CPK difference across the heart widened significantly (Table VI) and calculated CPK output by the heart increased seven to eightfold ( $p < 0.05$ ) in all groups.

Estimated blood flow to the normal myocardium (Table V) at one hour post occlusion was elevated; it was significantly increased ( $p < 0.05$ ) to both endocardial and epicardial layers in Groups II and III and only to the epicardial layer



**Fig 2** Time course of changes in left ventricular parameters (cardiac output, dP/dt and end-diastolic pressure [mean  $\pm$  SEM]) following coronary occlusion and following the exchange transfusions. Symbols as in Fig 1.

in Group I. Blood flow to the endocardial layers of the ischemic zone was reduced to approximately 32% ( $p < 0.05$ ) of the preocclusion value while epicardial flow was 37 to 40% of the control value. The transmural flow distribution was significantly reduced in Group I only (endo/epi flow ratio =  $0.83 \pm 0.07$ ) in contrast to Groups II and III (endo/epi ratios of  $0.89 \pm 0.11$  and  $0.93 \pm 0.09$  respectively). Perfusion of the marginal zone was somewhat better than that of the ischemic zone at this time; mean endocardial flow ranging from 36 to 40% and mean epicardial flow ranging from 39 to 49% of the respective control values. The transmural distribution of flow was significantly reduced in Group I only ( $1.06 \pm 0.07$  to  $0.80 \pm 0.10$ ,  $p < 0.05$ ).

**3 Effects of the exchange transfusions** The three different types of exchange transfusion produced significant differences between the three groups in terms of oxygen parameters in arterial blood (Tables II to IV). The hematocrit was reduced to 26 to 28% in Groups I and III while it remained at about 48% in the blood control group (Group II). In spite of the approximately equal hematocrit Groups I and III differed in terms of O<sub>2</sub> capacity and content in the plasma phase; in the former O<sub>2</sub> capacity was nearly 5 ml/dl in contrast to that in Group III (approximately 0.6 ml/dl). As a result of the oxygen carried in the plasma phase total O<sub>2</sub> content in arterial blood was about 4 ml/dl higher in Group I than in Group III although it was still 5 ml/dl lower than in the undiluted blood of Group II. In other respects blood

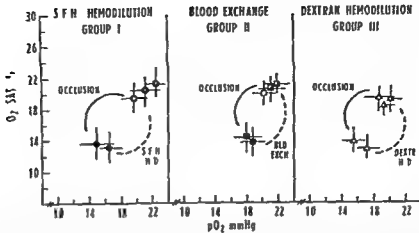


Fig 3 Changes in coronary sinus  $pO_2$  and  $O_2$  saturation (mean  $\pm$  SEM) in the three groups. Open symbols indicate the values in the pre-occlusion control state; filled symbols are those obtained at 30 and 60 minutes following coronary occlusion and the half filled symbols are those values obtained at 30 and 60 minutes after the exchange transfusions.

Table V Myocardial blood flow (ml/g/min) (mean  $\pm$  SEM) measured by microspheres in the three groups before and after coronary occlusion and after the exchange transfusion in different regions of the heart

Period	Pre occlusion control			1 hr post-occlusion			1 hr post-exchange		
Group	I	II	III	I	II	III	I	II	III
Ischemic zone									
Endo	1.12 $\pm$ .71	1.29 $\pm$ .23	1.19 $\pm$ .17	0.21 $\pm$ .19	0.34 $\pm$ .31	0.37 $\pm$ .17	0.64 $\pm$ .13	0.38 $\pm$ .09	0.59 $\pm$ .12
Epi	1.04 $\pm$ .14	1.19 $\pm$ .17	1.07 $\pm$ .20	0.27 $\pm$ .20	0.40 $\pm$ .14	0.40 $\pm$ .20	0.61 $\pm$ .14	0.44 $\pm$ .10	0.63 $\pm$ .17
Endo/epi ratio	1.08 $\pm$ .09	1.09 $\pm$ .11	1.12 $\pm$ .09	0.83 $\pm$ .07	0.89 $\pm$ .11	0.93 $\pm$ .09	1.04 $\pm$ .12	0.89 $\pm$ .13	0.94 $\pm$ .11
Marginal zone									
Endo	1.17 $\pm$ .16	1.23 $\pm$ .18	1.29 $\pm$ .21	0.43 $\pm$ .13	0.48 $\pm$ .20	0.52 $\pm$ .14	0.81 $\pm$ .12†	0.51 $\pm$ .17	0.61 $\pm$ .15
Epi	1.10 $\pm$ .27	1.14 $\pm$ .24	1.22 $\pm$ .23	0.54 $\pm$ .10	0.47 $\pm$ .13	0.48 $\pm$ .13	0.67 $\pm$ .11†	0.59 $\pm$ .12	0.69 $\pm$ .17
Endo/epi ratio	1.06 $\pm$ .09	1.09 $\pm$ .09	1.06 $\pm$ .11	0.80 $\pm$ .10	1.02 $\pm$ .09	1.00 $\pm$ .09	1.21 $\pm$ .14	0.88 $\pm$ .13	0.88 $\pm$ .11
Normal zone									
Endo	1.27 $\pm$ .14	1.38 $\pm$ .19	1.31 $\pm$ .27	1.43 $\pm$ .15	1.80 $\pm$ .11	1.78 $\pm$ .17	2.67 $\pm$ .19	1.78 $\pm$ .19	2.79 $\pm$ .13
Epi	1.21 $\pm$ .17	1.32 $\pm$ .21	1.09 $\pm$ .17	1.54 $\pm$ .17	1.66 $\pm$ .08	1.34 $\pm$ .21	3.71 $\pm$ .11	1.71 $\pm$ .17	2.64 $\pm$ .16
Endo/epi ratio	1.05 $\pm$ .14	1.05 $\pm$ .09	1.20 $\pm$ .14	0.96 $\pm$ .09	1.11 $\pm$ .08	1.33 $\pm$ .10	0.99 $\pm$ .09	1.04 $\pm$ .07	1.06 $\pm$ .08

Indicates statistically significant ( $P < .05$ ) change by paired  $t$  test from the pre-occlusion value.

†Indicates statistically significant ( $P < .05$ ) change by paired  $t$  test from the 60 minute post-occlusion value.

Table VI Comparison of arterial coronary sinus CPK differences and calculated CPK output at various times in the three groups

Group	Aortic coronary sinus C.P.K. $\Delta$ (mU/ml)			C.P.K. output (mU/g heart wt/min.)		
	I	II	III	I	II	III
Pre occlusion	72 $\pm$ 41	81 $\pm$ 32	79 $\pm$ 43	87 $\pm$ 30	97 $\pm$ 49	9.5 $\pm$ 37
30 post-occlusion	27 $\pm$ 6	32 $\pm$ 7	37 $\pm$ 9			
60 post-occlusion	47 $\pm$ 10	31 $\pm$ 11	46 $\pm$ 12	70.5 $\pm$ 12.1	68.8 $\pm$ 14.1	78.2 $\pm$ 17.1
30 post-exchange	31 $\pm$ 14	67 $\pm$ 15	47 $\pm$ 14			
60 post-exchange	27 $\pm$ 9	71 $\pm$ 19	60 $\pm$ 13	50.9 $\pm$ 9.1	121 $\pm$ 29†	152 $\pm$ 31†

$p < .05$  by paired  $t$  test from pre-occlusion control.

† $p < .05$  by paired  $t$  test from 60 minute post-occlusion value.

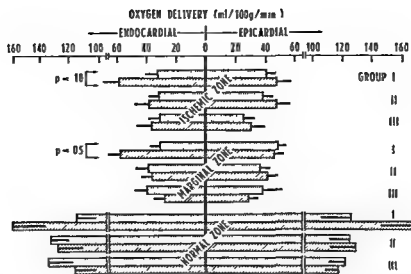


Fig 4 Summary of the changes (mean  $\pm$  SEM) in myocardial oxygen delivery in the three experimental groups. For the sake of simplification the pre occlusion values were omitted. *stippled bars* indicate the measurements made at 60 minutes post occlusion while the *cross hatched bars* indicate the measurements made at the 1 hour post infusion (i.e. 2 hours post occlusion) period. Note the statistically significant increase in subendocardial O<sub>2</sub> delivery in the marginal zone in Group I. Note break in scale to accommodate higher values in the normal zone.

parameters were similar in the three groups.

In hemodynamic terms (Figs 1 and 2) only two significant trends were evident between the groups. Firstly, only Group III subjected to dextran hemodilution exhibited elevated ( $p < 0.05$ ) cardiac output when compared to the other groups. Secondly, Group I exhibited a significantly raised  $dP/dt$  as compared to the post occlusion depressed levels but only at two of the measurement periods. Two minor and not statistically significant differences were also evident. Group I showed the most marked fall in arterial blood pressure and the lowest LVEDP.

The effects of the exchange transfusions on blood parameters in the coronary sinus are summarized in Fig 3. Surprisingly, a rise of approximately equal magnitude in  $pO_2$  and  $O_2$  saturation occurred in all three groups returning these parameters to within the preocclusion range. This was an unexpected finding in at least Group II.

Blood flow to the normal myocardium (Table V) rose only marginally in Group II while it increased significantly ( $p < 0.05$ ) in both hemodiluted groups (Groups I and III). These increments were of such magnitude that the calculated  $O_2$  delivery was maintained at essentially the control level. In contrast in the ischemic and marginal zones, although there were significant increments in blood flow (Table V),  $O_2$  delivery

was restricted (Fig 4) in all three groups with two notable exceptions. In Group I, endocardial  $O_2$  delivery after hemodilution with SFH was nearly significantly ( $0.10 > p > 0.05$ ) higher in the ischemic zone and it was significantly ( $p < 0.05$ ) higher in the marginal zone when compared to the pre hemodilution level in the same animals as well as when compared to the post exchange transfusion values in the other groups. The data indicate a significant improvement in endocardial perfusion following hemodilution with SFH in the normal as well as in the ischemic myocardium.

One hour following the exchange transfusion, the washout of CPK from the heart (Table VI) increased significantly in Groups II and III but was reduced in Group I, although the decrement itself in the latter group did not attain significance in itself ( $p = 0.10$ ). The numerical value in Group I was significantly ( $p < 0.05$ ) lower than those found at the same time in the other groups. The weights of the three zones of myocardium prior to their digestion in KOH are compared in Table VII. Since the mean values of the total left ventricular weights were somewhat different in the three groups, comparison on a percentage basis indicates that the ischemic and marginal zones were somewhat smaller in Group I. This may indicate an apparent underestimation of these zones because of a difficulty in visual

Table VII Weights of the three zones of myocardium in the three groups

	Group I	Group II	Group III
Ischemic zone			
Weight	159 $\pm$ 17 g	253 $\pm$ 14 g	219 $\pm$ 31 g
% of whole L.V	148 $\pm$ 14%	223 $\pm$ 09%	181 $\pm$ 26%
Marginal zone			
Weight	64 $\pm$ 19 g	88 $\pm$ 07 g	97 $\pm$ 12 g
% of whole L.V	54 $\pm$ 17%	74 $\pm$ 06%	80 $\pm$ 10%
Normal zone			
Weight	91.8 $\pm$ 11.2 g	80.5 $\pm$ 10.0 g	89.7 $\pm$ 10.7 g

demarcation in the animals hemodiluted with SFH. This is reflected in the somewhat lower blood flow (especially in the endocardial layer) found in the ischemic zone in this group at the one hour post occlusion period indicating that this zone may have been underestimated in comparison with the other groups.

### Discussion

A solution of hemoglobin would have many of the characteristics of a potentially ideal plasma expander or blood substitute: colloid osmotic effects, oxygen transporting and releasing capability, stability in storage greater than that of whole bank blood, absence of type specific and non specific antigens and of viral contaminants. Over the past half century a number of attempts have been made to produce suitable hemoglobin solutions<sup>2</sup> with limited success. More recently the undesirable side effects (impaired coagulation and renal function) have been shown to be largely due to stroma fragments and their removal eliminated most of these effects<sup>3</sup>. The potential usefulness of stroma free hemoglobin solution was illustrated by Moss and associates<sup>4</sup> who demonstrated that apparently bloodless baboons could survive a complete exchange transfusion with a hematocrit of less than 3%.

The rationale for the hypothesis tested in the present experiments can be appreciated against the following background: it is now increasingly recognized that the rheological properties of blood play a pivotal role in determining nutritive capillary flow. These rheological properties are mainly determined by the hematocrit and the physical conditions of flow. The viscosity of whole blood is related to the hematocrit in an apparently exponential manner so that a given increment in hematocrit produces increasingly greater rises

in viscosity as the initial hematocrit increases<sup>5,6</sup>. This is partly due to the fact that erythrocytes increasingly tend to aggregate forming larger and less easily deformed particles as the hematocrit increases<sup>7</sup>. The tendency to aggregation is opposed by the shearing forces to which blood is subjected during flow; the extent of disaggregation is primarily a function of the prevailing shear rate<sup>8</sup>. At the relatively low shear rates prevailing in the microcirculation especially during conditions of a reduction in the driving pressure gradient and flow (e.g. hypotension or coronary artery stenosis), the tendency to aggregation becomes dominant and a vicious circle of increasingly impaired nutritive perfusion of the microcirculation follows<sup>9</sup>.

Under a given set of prevailing conditions (perfusion pressure, vascular hindrance, shear rate) in a given vascular bed the resistance to blood flow is a direct function of blood viscosity. Thus collateral perfusion in the absence of autoregulation would be largely determined by blood viscosity. Clinical studies in patients with fresh myocardial infarction have demonstrated increased blood viscosity and significant deterioration in rheological properties of blood<sup>10,11</sup>. Under controlled experimental conditions a significant and progressive rise in blood viscosity occurs within one hour of a sudden coronary occlusion in the dog. This renders the observable collateral perfusion of the ischemic myocardium less than optimal and a reduction in blood viscosity appears desirable. Hemodilution with SFH was shown not only to reduce the blood viscosity in proportion to the reduction in hematocrit but to produce a blocking effect of the rise in observed viscosity and erythrocyte aggregation accompanying acute myocardial ischemia<sup>12</sup>. This combination of rheological effects with the oxygen

transporting and releasing capacity of SFH and its effects on improving subendocardial perfusion in the non ischemic heart<sup>16</sup> have lead to the present experiments

Two other characteristics of SFH must be considered namely its short intravascular retention and its high affinity for oxygen. Unprotected by the erythrocyte membrane the unaltered hemoglobin molecule in solution in the plasma disappears fairly rapidly from the circulation its half life in the dog is 2 to 3 hours.<sup>17</sup> It is for this reason that our experiments were of short duration only. The benefits however, could be sustained by a continuous infusion. Secondly in the absence of the intraerythrocytic regulators of hemoglobin oxygen affinity<sup>18</sup> SFH releases its oxygen less readily than erythrocytic hemoglobin.<sup>19, 20</sup> "This would appear to be a disadvantage. However the relatively hypoxic and acidotic environment of ischemic myocardium would be expected to induce O<sub>2</sub> release from plasma phase hemoglobin as well.

The quantitative estimation of the mass of ischemic myocardium is difficult. The most successful estimator is that pioneered by Sobel and co workers<sup>21</sup> utilizing the estimation of total CPK released. For a variety of practical reasons this was not possible in our experiments. Our results also illustrate a variety of obvious difficulties. The choice of the dog as experimental animal may be questioned because of its extensive and variable coronary collateral circulation. Yet this animal is the most frequently used model in this area. We tried to avoid any bias by the random assignment of animals to the three treatment groups. There was also obvious difficulty in the precise visual demarcation of the ischemic and marginal zones. It appears that these zones were underestimated in Group I. Clearly this difficulty and the heterogeneity of myocardial perfusion contributed to the differences between the groups. The underestimation of the ischemic zone in Group I resulted in comparison of a more ischemic core with a more restricted collateral perfusion than those in Groups II and III. Nevertheless subendocardial O<sub>2</sub> delivery in the former was significantly improved by hemodilution with SFH.

In spite of these difficulties the experiments revealed three lines of circumstantial evidence pointing to an improved collateral perfusion of

the marginally ischemic myocardium particularly to the subendocardial layers following hemodilution with SFH. Firstly, Group I exhibited the greatest increment in subendocardial blood flow and in O<sub>2</sub> delivery. Secondly, in contrast to the increasing output of CPK in Groups II and III there was a reversal of this trend in Group I. Presumably this indicates a reduction in the mass of myocardium leaking the enzyme. Although the majority of CPK measurable in peripheral blood gets there by way of the cardiac lymph the actual estimation of direct washout of this enzyme by the collateral blood flow must bear some relation to a mass intensity product of myocardial damage. Thirdly, although statistically not consistently significant, Group I exhibited the best left ventricular performance returning to the pre occlusion level. While a strict linear relationship between the extent of myocardial ischemia and performance may not exist some correlation has been demonstrated<sup>22, 23</sup> and it is reasonable to expect that the extent of functional limitation is related to the mass of ischemic myocardium.

There is a further possibility of a passive mechanical factor contributing to the improved collateral perfusion. Flow in maximally dilated vessels as these collaterals presumably are is also proportional to the left ventricular end diastolic pressure because of the vascular waterfall phenomenon.<sup>24</sup> As a result of the lower end diastolic pressure in Group I there is less compression than in the other groups allowing better perfusion through the maximally dilated collaterals. The fact that a similar phenomenon is not seen in the Dextran hemodiluted group (Group III) suggests that a factor other than reduced impedance to ejection is also involved.

Blood parameters measured in the coronary sinus revealed no significant differences between the groups. The pO<sub>2</sub> and oxy hemoglobin saturation in coronary sinus blood reflects the integrated effects of a spectrum of oxygen extraction by various regions of the myocardium. Because of the shape of the oxy hemoglobin dissociation curve hyperperfused areas tend to dominate the effects of hypoperfused areas. The initial decrease in coronary sinus pO<sub>2</sub> following the occlusion reflected the low pO<sub>2</sub> of the blood draining from the poorly perfused areas. The subsequent rise in pO<sub>2</sub> in all the groups appears to

reflect two effects: redistribution of myocardial flow with increased perfusion of the normal myocardium and a subsequent improvement with time in collateral perfusion of the ischemic myocardium. Although the normal myocardium assumes the work share<sup>3</sup> and oxygen cost of the ischemic regions, the increased flow to the normal myocardium may have permitted a rise in  $pO_2$  and  $O_2$  saturation of the blood draining from these regions thereby diluting the relatively small volume of low  $pO_2$  blood draining from the ischemic regions. A second possibility is that of a spontaneous improvement with time in collateral perfusion of the ischemic myocardium and a rise in oxygen saturation and  $pO_2$  in the blood draining therefrom. This possibility is only partly supported by the flow measurements in Group II although there was no significant increase in blood flow to the ischemic core; there was in fact a modest flow increment (26%) in the epicardial layers of the marginal zone. Similar changes in coronary sinus blood were seen in the other groups as well but it is not quite clear what mechanism accounts for the observed changes and they may not necessarily reflect changes in tissue  $pO_2$  in the different regions of the heart.

It appears that these findings based on an expectation of rheological improvement are suggestive of some improvement in collateral perfusion of the ischemic myocardium. This would warrant further experimental exploration of the possible therapeutic benefits of hemodilution with SFH.

### Summary

The effect of hemodilution with stroma free hemoglobin (SFH) solution was assessed on the collateral perfusion of acutely ischemic myocardium in anesthetized dogs. A similar protocol was used in three groups: one hour following occlusion of the LAD coronary artery, a rapid exchange transfusion was performed and the changes were followed for the subsequent two hours. Group I was hemodiluted with SFH; in Group II whole blood was reinfused; and Group III was hemodiluted with dextran 70. Following the exchange transfusions, blood flow to the ischemic zone ( $15 \pm 3 \mu\text{m}$  microspheres) increased in all groups but only marginally so in Group II ( $23 \pm 17\%$ ). The greatest increments were seen in the SFH hemodiluted group (Group I) in which endocar-

dial flow increased by  $83 \pm 29\%$  ( $p < 0.05$ ) and epicardial flow increased by  $45 \pm 21\%$ ; these resulted in the greatest improvements in oxygen delivery. Significant increments in blood flow were seen in Group III as well but oxygen delivery was less adequate. Group I also exhibited the lowest output of CPK from the heart and was the only one in which indices of left ventricular performance ( $dP/dt$  and EDP) were returned to the pre occlusion level. These findings suggest the possibility that reduction of blood viscosity by dilution with SFH improves collateral perfusion of the ischemic myocardium.

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### Note added in proof

In the interval following submission and acceptance of this paper, another report has appeared (Feola M, Azar D and Wiener L. Improved oxygenation of ischemic myocardium by hemodilution with stroma free hemoglobin solution. *Chest* 75:369, 1979) reporting essentially similar findings. These authors observed that a similar procedure of hemodilution with SFH resulted in improvement in myocardial tissue  $pO_2$  and a reduction in the presumptive infarct volume when compared to that seen following hemodilution with dextran or the reinfusion of whole blood. This and the present paper are thus in substantial agreement on the apparently beneficial effects of this procedure upon myocardial ischemia.

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## Rest and exercise hemodynamics in children before and after aortic valvotomy

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Valvar aortic stenosis is a relatively common congenital heart lesion presenting in childhood. Aortic valvotomy is usually recommended for affected children with symptoms such as angina or syncope or with hemodynamic evidence of moderately severe or severe aortic stenosis.

In this study the rest and exercise hemodynamics in a group of children with moderate or severe congenital valvar aortic stenosis are compared before and after aortic valvotomy to determine changes occurring as a result of valvotomy.

### Materials and methods

Eighteen patients 13 males and five females with valvar aortic stenosis were studied by cardiac catheterization at rest both before and after aortic valvotomy.

Aortic valvotomy was performed using cardiopulmonary bypass. In 15 patients with bicuspid valves both commissures were incised as far as possible toward the annulus without producing significant aortic incompetence. In the two patients with a unicommissural valve only the single commissure was incised. In the remaining patient with a tricuspid valve and fused commissures two commissures were incised.

The age of the patients at the time of preoperative catheterization ranged from 3 months to 17 years (mean of 10.8 years). Aortic valvotomy was

performed from 1 to 5 months following the initial cardiac catheterization (mean of 2.8 months). Postoperative catheterization was performed within 3 years of operation in 16 patients and 3 and 10 years postoperatively in the remaining two patients.

Cardiac catheterization was performed with the patient in a fasting state following premedication with phenobarbital and morphine. The left heart pressures were measured with a NIH angiography catheter or Statham transducer tipped catheter. Right sided pressures were measured using a Goodale Lubin catheter. The pressures were recorded on an Electronics for Medicine recorder using a Statham 23db pressure transducer for fluid filled catheters.

Cardiac output was determined utilizing the Fick principle. In 15 of the patients preoperatively and in each of the patients postoperatively oxygen consumption was measured by collecting the patient's expired air in a Tissot spirometer. The expired gas was analyzed for O<sub>2</sub> and CO<sub>2</sub> content. Oxygen consumption was calculated by standard methods. In the remaining three patients preoperatively oxygen consumption was estimated as 160 cc O<sub>2</sub>/min/M. Midway during the measurement of oxygen consumption the left ventricular end diastolic pressure (LVEDP) and peak left ventricular systolic pressure were recorded. The catheter tip was withdrawn from the left ventricle into the aorta while the pressure was recorded and measured continuously.

During the measurement of oxygen consumption blood samples were withdrawn simultaneously from the pulmonary artery and the aorta. Oxygen content (O<sub>2</sub>) of these blood samples was determined either by the Van Slyke method or calculated from determinations of oxygen saturation.

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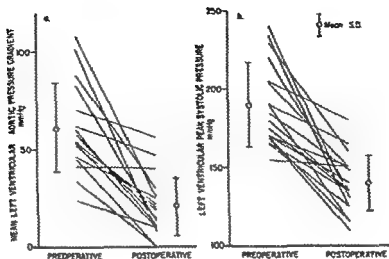


Fig 1 Pre- and postoperative mean left ventricular aortic pressure gradient (a) and left ventricular systolic pressure (b) at rest

tion hemoglobin and partial pressure of oxygen ( $pO_2$ ) using the formula  $O_2 = 1.36 \times \text{hemoglobin} \times \% \text{ saturation} + 0.003 \times pO_2 \text{ mm Hg}$

Ten of the 18 patients were exercised both pre and postoperatively on a variable resistance bicycle ergometer at work loads ranging from 30 to 100 watts. The work load was chosen so that the patient could continue to exercise for three to six minutes without fatigue and with a heart rate of approximately double the resting heart rate. After a constant work load and heart rate had been maintained for several minutes cardiac output was determined by the Fick method and LVEDP, left ventricular systolic and aortic pressures were again measured.

For both rest and exercise stroke volume was calculated by dividing cardiac output by the heart rate. The stroke volume and cardiac output were indexed for body surface area. Stroke work index (SWI) was calculated by the formula  $SWI (\text{gm m}^2/\text{m}^2) = (SI \times 1.055) (LV - LVEDP) \times 13.6/1000$  where  $LV$  = peak left ventricular systolic pressure and  $SI$  = stroke index. The aortic valve area was calculated from the mean left ventricular aortic gradient and cardiac output was calculated using the formula of Gorlin and Gorlin. The aortic valve area was indexed for body surface area.

The ratio of the diastolic pressure time interval (DPTI)  $\times$  arterial oxygen content ( $O_2$ ) to systolic pressure time interval (SPTI) was used as an indirect measure of subendocardial blood flow. For this calculation the left ventricular systolic and diastolic pressure time intervals were calcu-

lated from pressure tracings by planimeterization of the superimposed left ventricular and aortic pressure tracings using the method outlined by Lewis and co workers.

The presence of aortic insufficiency was evaluated semiquantitatively from cineangiograms recorded after the injection of radiopaque contrast material (1 to 2 cc/kg) into the ascending aorta approximately 2 cm above the aortic valve. The degree of aortic insufficiency was graded 1 to 4+. Adequate pre and postoperative aortic cineangiograms were available in 15 of the 18 patients.

The comparison of pre and postoperative values for the measured and calculated parameters and the comparison of the resting and exercise data was made by the paired  $t$  test.

## Results

The pre and postoperative data of the 18 patients studied at rest are shown in Table I. The pre and postoperative data of ten of the 18 patients studied at both rest and exercise are shown in Table II.

**Resting hemodynamics** The resting heart rate and oxygen consumption before and after aortic valvotomy are not significantly different ( $p > 0.1$ ) indicating that the patients were in comparable resting hemodynamic states at the time of each cardiac catheterization.

Although there were no significant differences in the cardiac indices before and after surgery, the cardiac indices of individual patients varied. No patient had a cardiac index below normal limits.

Table 1 Resting hemodynamics

		BSA	CI	HR	SI	LVEDP	LVPSP	Mean Gradient	AVA	SPTI
I	Pre	1.75	4.3	70	51	13	190	60	0.52	3164
	Post	1.84	2.9	80	36	14	115	11	0.76	2597
II	Pre	1.70	3.9	70	56	12	180	57	0.49	3716
	Post	1.77	3.2	68	47	12	135	13	0.79	2611
3	Pre	1.13	4.8	80	60	8	170	52	0.61	3568
	Post	1.65	4.7	96	49	12	140	19	0.84	2957
4	Pre	1.06	3.6	84	42	14	175	59	0.48	3494
	Post	1.06	4.7	80	59	12	135	10	1.06	25.6
5	Pre	1.0	4.2	72	58	12	170	34	0.74	2980
	Post	1.12	2.9	70	41	11	115	5	—	2541
6	Pre	1.70	3.6	72	50	13	155	53	0.44	3283
	Post	1.73	3.9	66	59	14	150	10	1.16	3459
7	Pre	1.35	5.4	110	49	13	185	45	0.57	3938
	Post	1.53	4.6	120	38	12	148	0	—	2004
III	Pre	0.92	4.3	96	45	14	190	62	0.50	3610
	Post	1.0	7.1	100	71	13	165	47	0.81	3520
9	Pre	1.51	4.9	78	63	13	165	46	0.67	3463
	Post	1.63	3.7	80	46	16	135	25	0.64	2997
10	Pre	0.94	5.3	100	53	12	170	53	0.53	3400
	Post	1.15	5.1	100	51	11	120	21	0.97	2600
11	Pre	1.06	3.9	90	43	11	240	89	0.31	4608
	Post	1.10	4.3	78	55	12	130	30	0.72	2738
III	Pre	1.41	6.7	96	70	12	243	101	0.55	3971
	Post	1.52	4.3	90	48	13	128	8	1.16	2880
III	Pre	1.18	3.9	80	49	11	230	83	0.36	4560
	Post	1.23	4.4	78	66	15	160	13	1.1	3687
14	Pre	0.28	4.5	180	25	8	220	108	0.36	6120
	Post	0.86	3.2	90	36	12	135	26	0.52	3096
15	Pre	0.96	4.0	84	48	13	155	24	0.64	3041
	Post	1.03	5.5	104	53	12	125	10	1.60	4160
16	Pre	0.87	7.6	108	70	14	205	70	0.69	3807
	Post	0.96	5.3	90	59	14	180	56	0.63	3744
17	Pre	0.86	3.6	100	34	10	170	41	0.41	4200
	Post	1.60	3.2	102	31	10	150	40	0.39	3590
18	Pre	1.30	5.8	100	58	12	210	54	0.64	4640
	Post	1.30	3.8	66	58	18	148	20	0.80	2831
Pre	Mean	1.17	4.7	93	51.9	11.9	189.7	60.6	0.53	3839.9
	STD Dev	±0.37	±1.1	±25.0	±11.5	±1.8	±27.2	±22.3	±0.12	±777.7
Post	Mean	1.34	4.3	87	49.6	12.9	139.7	20.2	0.87	3048.1
	STD Dev	±0.37	±1.1	±15.1	±10.4	±1.95	±17.4	±15.2	±0.3	±571.4

Pre = preoperative Post = postoperative BSA = body surface area M CI = cardiac index L/min/M HR = heart rate beats/min SI = stroke index cc/M LVEDP = left ventricular end-diastolic pressure mm Hg LVPSP = left ventricular peak systolic pressure mm Hg AVA = aortic valve area cm<sup>2</sup>/m SPTI = systolic pressure time index mm Hg sec/min DPTI = diastolic pressure time index mm Hg sec/min  $\bar{O}_2$  = arterial oxygen content vol% NA = not available

(28 L/min/M) in either the pre- or the postoperative state. The mean resting cardiac index both before the surgery ( $4.7 \pm 1.1$  L/min/M<sup>2</sup>) and after valvotomy ( $4.3 \pm 1.1$  L/min/M<sup>2</sup>) was above the expected normal ( $3.5 \pm 0.7$  L/min/M<sup>2</sup>) suggesting that the children were not in a basal state at the time of cardiac catheterization.

The LVEDP was not significantly altered by

surgery. Eight patients preoperatively had an LVEDP greater than 12 mm Hg usually to levels of 13 or 14 mm Hg. In the other ten patients the LVEDP preoperatively was 12 mm Hg or less. In most of the patients only a minor change of 1 to 2 mm occurred following operation and over all there was no significant change. Eight patients postoperatively had an LVEDP greater than 12 mm Hg including five whose values were greater

DPTI	DPTI x 100		Aortogram
	SPTI		
2772	18	0	
2590	204	1+	
2688	15.2	1+	
2448	18.7	2+	
2337	12.0	<1+	
2515	14.5	<1+	
2755	13.8	0	
2458	16.6	0	
1800	10.3	NA	
2796	17.0	3+	
2218	13.5	0	
2917	17.8	3+	
2332	11.7	1+	
1344	11.2	4+	
2074	9.1	<1+	
2220	9.5	2+	
2058	14.7	0	
1646	9.3	3+	
2080	9.8	0	
1920	12.3	2+	
2178	7.6	0	
2184	12.8	2+	
2704	9.5	0	
2124	13.5	1+	
2978	11.3	<1+	
3432	16.4	1+	
2180	6.0	NA	
2134	11.4	2+	
2369	14.0	0	
2662	11.4	1+	
1649	7.3	0	
1636	7.2	1+	
2310	9.6	NA	
1816	8.2	0	
2080	7.8	0	
2501	14.4	2+	
2338.2	11.1		
± 387	3.3		
2769	13.5		
± 497.3	3.8		

than 12 mm Hg preoperatively. Three patients (Cases 9, 13 and 18) had a larger increase in the LVEDP after surgery (13 to 16 mm Hg, 11 to 15 mm Hg and 12 to 18 mm Hg respectively). The pre and postoperative resting LVEDP showed no significant correlation with age, left ventricular aortic mean gradient or aortic valve area.

The mean left ventricular aortic pressure gradient was significantly reduced by valvotomy ( $p < 0.01$ ) from a preoperative mean gradient of  $60.6 \pm 22.3$  mm Hg to a postoperative mean

gradient of  $20.2 \pm 15.2$  mm Hg (Fig 1). A similar significant reduction also occurred in peak left ventricular systolic pressure following surgery (Fig 1).

Although most patients showed a decrease in the resting mean left ventricular aortic pressure gradient, three of the 18 patients studied at rest (Cases 8, 16 and 17) had only a minor reduction in the resting mean gradient from a preoperative gradient of 62, 70 and 41 mm Hg to a postoperative gradient of 47, 56 and 40 mm Hg respectively. This indicated significant residual obstruction.

Preoperatively the aortic valve area at rest was less than  $0.7 \text{ cm}^2/\text{M}^2$  in 17 of the 18 patients (mean of  $0.53 \pm 0.12 \text{ cm}^2/\text{M}^2$ ). The remaining patient had an aortic valve area of  $0.74 \text{ cm}^2/\text{M}^2$  (Case 3). Postoperatively aortic valve area calculated on the basis of the Fick cardiac output was significantly increased to a mean value of  $0.87 \pm 0.3 \text{ cm}^2/\text{M}^2$  (Fig 2). Two patients had no residual gradient and so aortic valve area was not calculated. The postoperative valve area since it is based on cardiac output calculated by the Fick principle underestimates the valve area in those patients with a significant degree of aortic insufficiency.

In three patients (Cases 14, 16 and 17) the postoperative aortic valve areas were 0.52, 0.63 and  $0.39 \text{ cm}^2/\text{M}^2$  respectively. These showed minimal change from the preoperative values. Each of these three patients is considered to have major residual stenosis since none had a major degree of aortic insufficiency and the calculated aortic valve area was still small. In patient No. 9 the calculated postoperative aortic valve area was  $0.64 \text{ cm}^2/\text{M}^2$ ; this patient had fairly severe aortic insufficiency and recalculation of the aortic valve area using forward stroke volume based on left ventricular volume studies gave a valve area of  $1.12 \text{ cm}^2/\text{M}^2$ .

The incidence and severity of aortic incompetence increased after aortic valvotomy. Prior to surgery ten patients had no aortic incompetence noted on aortic angiography. In five others 1+ aortic regurgitation was recognized by cineangiography. In the remaining three patients although aortic cineangiograms were not performed there was no clinical evidence of aortic insufficiency. Postoperatively only two of the 18 patients studied by cineangiography showed no aortic incompetence (Table I). Among the other

Table II Exercise hemodynamics

		HR beats/min		VO cc/min/M <sup>2</sup>		CI L/min/M		Mean LV Ao gradient		LV PSP mm Hg	
		R	E	R	E	R	E	R	E	R	E
I	Pre	70	120	151	677	4.3	6.6	60	60	190	270
	Post	80	140	146	933	2.9	8.0	11	15	11	160
II	Pre	70	130	192	710	3.9	9.2	57	81	180	240
	Post	68	120	166	706	3.2	5.9	13	43	135	18
III	Pre	80	150	171	846	4.8	9.6	52	51	170	210
	Post	96	150	146	818	4.7	8.4	19	22	140	180
4	Pre	84	180	160	872	3.6	6.9	59	112	175	210
	Post	80	180	166	1071	4.7	8.6	15	42	135	180
5	Pre	72	150	169	762	4.7	8.4	34	64	170	240
	Post	70	120	167	710	2.9	6.7	8	8	115	160
6	Pre	72	132	169	768	3.6	7.8	53	59	155	200
	Post	66	130	204	783	3.9	9.0	10	8	140	160
7	Pre	110	170	173	785	5.4	8.3	45	55	185	270
	Post	120	155	211	710	4.6	7.0	0	0	148	185
8	Pre	96	150	148	505	4.3	7.7	62	62	190	240
	Post	100	140	212	602	7.1	10.4	47	60	165	270
9	Pre	78	138	164	623	4.9	7.7	46	9	165	230
	Post	80	132	154	68	3.7	6.1	25	37	135	180
10	Pre	100	150	193	768	5.3	8.0	53	95	170	230
	Post	100	155	152	692	5.1	7.4	21	28	120	150
Pre Mean			147	169	734.6	—	8.0	52.1	73.4	170	230
Pre STDDev			±18	±14.9	112.3	—	±0.9	±8.5	±20.9	±11.3	±19.4
Post Mean			142	172.4	760	—	7.8	16.1	24.7	135	1.6
Post STDDev			±18.4	±26.6	±136	—	±1.4	±13.6	±21.0	±16.1	±20.0

HR = heart rate VO = oxygen uptake cc/min/M CI = cardiac index LV Ao = left ventricular aortic pressure DPTI = diastolic pressure time interval SPTI = systolic pressure time interval O<sub>2</sub> = arterial oxygen content vol% SWI = stroke work index LVEDP = left ventricular end-diastolic pressure MI = stroke index AOA = aortic valve area

6° the degree of incompetence was assessed as 1+ in six patients 2+ in six patients and 3+ in four patients Two of the four patients with large regurgitant flows had a unicommissural valve at surgery the other two patients had bicuspid valves

DPTI × O<sub>2</sub>/SPTI was calculated to assess indirectly the subendocardial blood flow Of the 18 patients the preoperative resting DPTI × O<sub>2</sub>/SPTI ratio was less than 10 in eight patients and greater than 10 in the other ten patients For the entire group of patients flow ratio at rest correlated inversely with the mean gradient ( $r = -0.5$ ) LV pressure ( $r = -0.56$ ) and heart rate ( $r = -0.72$ ) The flow ratio did not correlate well with the aortic valve area ( $r = 0.17$ ) Following operation only four patients had a DPTI × O<sub>2</sub>/SPTI of less than 10 In three of these patients (Cases 8 16 and 17) the reduced ratio reflected residual obstruction since in each

patient the resting left ventricular aortic mean pressure gradient was 40 mm Hg or more after surgery In the fourth patient (Case 9) although the mean gradient was reduced there was a marked increase in the severity of aortic insufficiency For the entire group postoperatively there was a significant increase in the DPTI × O<sub>2</sub>/SPTI from a preoperative mean value of  $11.1 \pm 3.3$  to a postoperative mean value of  $13.5 \pm 3.8$  ( $p < 0.01$ ) (Fig 3) The increase in this ratio is related mainly to the reduction in systolic pressure time interval from a preoperative mean value of  $3.839.9 \pm 773$  to a postoperative mean value of  $3.048 \pm 521.4$  mm Hg sec/mm There was little change in the DPTI following surgery decreasing from  $2.338.2 \pm 382$  mm Hg sec/min to  $2.269.7 \pm 497.3$  mm Hg sec/min A slight decrease in DPTI may be related to the increased degree of aortic insufficiency and lowering of aortic diastolic pressure

DPTI		SPTI		$\frac{DPTI \times O}{SPTI}$		SWI gm/M /min		LV EDP mm Hg		SI cc/min /M		AVA cm. /M	
R	E	R	E	R	E	R	E	R	E	R	E	R	E
2222	2328	3146	5688	18.0	8.6	150.9	163.4	13	18	61	50	0.52	0.69
2560	2800	2592	4256	20.4	14.5	52.2	116.1	14	18	37	57	—	—
2688	2298	3276	6636	15.2	6.4	130.0	229.2	12	18	56	71	0.49	0.79
2448	2400	2611	4224	18.7	11.9	82.9	116.4	12	16	47	49	—	—
2392	2370	3468	5890	12.0	2	139.5	180.9	8	13	60	64	0.61	0.92
2015	3000	7957	4680	14.5	11.1	90.0	134.2	12	13	49	46	—	—
2755	2196	3494	6444	13.8	6.0	97.0	142.7	14	15	47	39	0.48	0.43
2488	2700	2076	5329	16.6	9.2	104.1	174.3	12	14	59	48	—	—
1800	2490	2980	5100	10.3	8.8	131.5	184.8	12	10	58	46	0.74	0.68
2296	2676	2541	4092	17.0	17.7	61.2	170.5	11	10	41	56	—	—
2218	2009	3283	5412	13.5	7.7	101.9	150.8	13	16	50	59	0.44	0.69
2917	3328	3457	5200	17.8	13.6	115.1	146.5	12	12	59	69	—	—
2332	2584	3938	5814	11.7	8.7	10.9	144.8	13	14	49	49	0.5	0.80
1344	2832	7304	5064	11.2	11.1	74.2	107.8	12	18	38	45	—	—
20.4	1952	3610	5348	9.1	5.4	113.6	166.1	14	13	45	51	0.50	0.64
2220	2160	3520	5400	9.5	6.5	154.8	214.5	13	18	71	74	—	—
3008	1794	3463	6348	14.7	5.0	13.4	174.4	13	13	63	56	0.67	0.57
1846	2296	2992	5.00	9.3	7.9	78.5	110.2	16	13	46	46	—	—
2080	1950	3400	6000	9.8	5.4	170.2	160.0	12	13	53	53	0.53	0.54
1970	2480	2600	4484	12.3	9.6	79.8	97.0	11	12	51	48	—	—
2416.9	2201	3417.6	5829	17.8	6.9	125.3	1.04	12.4	14.3	53.7	55.3	0.56	0.68
± 392.1	± 256.8	± 760.1	± 559.1	± 2.8	± 1.5	± 18.1	± 24.0	± 1.7	± 2.5	± 7.1	± 8.6	± 0.09	± 0.14
2235.0	2669	2814.4	4788	4.7	10.8	89.3	127.6	12.7	14.5	49.7	54.8	—	—
± 471.1	± 343.9	± 406.2	± 500.0	± 4.0	± 9.5	± 99.5	± 33.7	± 1.6	± 3.1	± 10.8	± 9.9	—	—

**Exercise hemodynamics before and after aortic valvotomy** In ten of the 18 patients rest and exercise hemodynamic studies were performed both before and after aortic valvotomy. The data on these patients are summarized in Table II.

The heart rate and oxygen consumption increase significantly from rest to exercise both pre and postoperatively ( $p < 0.01$ ). The levels of heart rate and oxygen consumption obtained preoperatively were not significantly different from the postoperative values suggesting that the level of exercise was similar. Each patient preoperatively and postoperatively showed an increase in cardiac index. The relationship between exercise cardiac index and the corresponding oxygen consumption was normal in all except one patient (Fig. 4).

The postoperative left ventricular aortic mean pressure gradient measured during exercise ( $24.7 \pm 21$  mm Hg) decreased significantly from the preoperative value during exercise ( $73.4 \pm 20.9$  mm Hg) (Fig. 5a). A significant

reduction ( $p < 0.01$ ) also occurred in the postoperative peak left ventricular systolic pressure during exercise from the preoperative exercise value of  $230 \pm 19.4$  mm Hg to the postoperative exercise value of  $176 \pm 20$  mm Hg (Fig. 5b). The postoperative increase in the left ventricular systolic pressure that occurred with exercise was significantly less after surgery than before.

During exercise the  $DPTI \times O / SPTI$  ratio decreased significantly from resting values both before and after operation ( $p < 0.01$ ). Prior to operation the  $DPTI \times O / SPTI$  ratio decreased from a mean value of  $12.8 \pm 2.8$  at rest to a value of  $6.9 \pm 1.5$  with exercise. Each of the ten patients had exercise ratios below 10 before surgery; in five patients the value was below 6.5. After surgery although the  $DPTI \times O / SPTI$  ratio still decreased with exercise the mean value during exercise ( $10.8 \pm 2.5$ ) was significantly higher than before surgery (Fig. 6). Postoperatively only four of ten patients had ratios of less than 10 during exercise and no patient had a value of



Table II Exercise hemodynamics

		HR beats/min		VO cc/min/M <sup>2</sup>		CI L/min/M		Mean LV Ao gradient		LV PSP mm Hg	
		R	E	R	E	R	E	R	E	R	E
1	Pre	70	170	151	6.7	4.3	6.6	60	60	190	270
	Post	80	140	146	9.33	2.9	8.0	11	15	115	160
2	Pre	70	130	192	7.0	3.9	9.2	57	81	180	240
	Post	68	120	166	7.05	3.2	5.9	13	43	135	185
3	Pre	80	150	171	8.6	4.8	9.6	57	51	170	210
	Post	96	150	146	8.18	4.7	8.4	19	22	140	180
4	Pre	84	180	160	8.2	3.6	6.9	59	112	175	270
	Post	80	180	166	10.34	4.7	8.6	15	42	135	180
5	Pre	72	150	169	7.62	4.2	8.4	34	64	170	240
	Post	70	120	167	7.10	2.9	6.7	0	0	115	160
6	Pre	72	132	163	7.68	3.6	7.8	53	59	165	200
	Post	66	130	204	7.83	3.9	9.0	10	0	160	160
7	Pre	110	170	173	7.8	5.4	8.3	45	55	185	270
	Post	120	155	211	7.10	4.6	7.0	0	0	148	185
8	Pre	96	150	148	5.0	4.3	7.7	62	67	190	240
	Post	100	140	212	6.02	7.1	10.4	47	60	165	220
9	Pre	78	138	164	6.73	4.9	7.7	46	95	165	230
	Post	80	132	154	6.8	3.7	6.1	25	37	135	180
10	Pre	100	150	193	7.68	5.3	8.0	53	95	170	230
	Post	100	155	152	6.22	5.1	7.4	21	28	120	150
Pre	Mean		147	169	7.34	—	8.0	52.1	73.4	175	230
	STDD		±18	±14.9	±12.3	—	±0.9	±8.5	±20.9	±11.3	±19.4
Post	Mean		147	172.4	7.0	—	7.8	16.1	24.7	135	166
	STDD		±18.4	±7.5	±13.6	—	±1.4	±13.6	±21.0	±16.1	±70.0

HR = heart rate VO = oxygen uptake cc/min/M CI = cardiac index LV Ao = left ventricular aortic LV PSP = left ventricular systolic pressure DPTI = diastolic pressure time interval SPTI = systolic pressure time interval O = arterial oxygen content vol. % SWI = stroke work index LVEDP = left end-diastolic pressure SI = stroke index A/A = aortic valve area

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DPTI  $\times$  O /SPTI was calculated to assess indirectly the subendocardial blood flow Of the 18 patients the postoperative resting DPTI  $\times$  O /SPTI ratio was less than 10 in eight patients and greater than 10 in the other ten patients For the entire group of patients flow ratio at rest correlated inversely with the mean gradient ( $r = -0.5$ ) LV pressure ( $r = -0.56$ ) and heart rate ( $r = -0.72$ ) The flow ratio did not correlate well with the aortic valve area ( $r = 0.17$ ) Following operation only four patients had a DPTI  $\times$  O /SPTI of less than 10 In three of these patients (Cases 8 16 and 17) the reduced ratio reflected residual obstruction since in each

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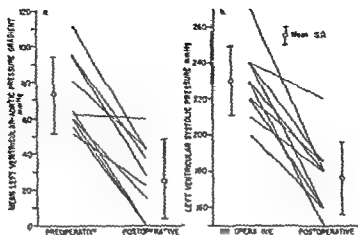


Fig 5 Pre and postoperative mean left ventricular aortic pressure gradient (a) and left ventricular systolic pressure (b) on exercise

exercise in spite of an increase of the LVEDP is abnormal and indicates persistent cardiac dysfunction

#### Discussion

Aortic valvotomy is the recognized treatment for children with severe aortic stenosis which is usually defined hemodynamically as an aortic valve area of less than  $0.5 \text{ cm}^2/\text{M}^2$  or a peak systolic left ventricular aortic pressure gradient greater than  $70 \text{ mm Hg}$ . Ideally, aortic valvotomy in children should be a low risk procedure should remove the known risk of sudden death, prevent the myocardial dysfunction seen in adults, and restore normal rest and exercise hemodynamics.

The operative mortality rate of aortic valvotomy is very low. Successful surgery significantly reduces the risk of sudden death. Although most of the patients show a significant reduction in the resting left ventricular aortic pressure gradient, some have major residual stenosis and many have a major increase in aortic insufficiency. Of our 18 patients, three had moderate or severe residual stenosis following valvotomy while another four had a major degree of postoperative aortic insufficiency. Although this is a selected group of patients, others have reported similar results. Thus Bernhard and associates<sup>1</sup> reported similar results in a large series of patients after aortic valvotomy. It is likely that the residual problems are related more to the pathologic anatomy of the aortic valve than to inadequate surgical technique. In patients with unicommissural valves, inadequate relief of steno-

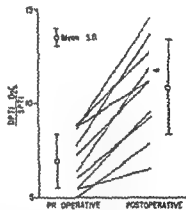


Fig 6 Pre and postoperative  $DPTI \times O_2/SPTI$  on exercise.  $DPTI$  = diastolic pressure time interval ( $\text{mm Hg} \cdot \text{sec}/\text{min}$ );  $SPTI$  = systolic pressure time interval ( $\text{mm Hg} \cdot \text{sec}/\text{min}$ );  $O_2$  = arterial oxygen content vol. %

sis or the development of severe valvular insufficiency may be inevitable.

The preoperative exercise hemodynamics in our study are similar to those which we have previously reported in a large series of children with aortic stenosis. The left ventricular systolic pressure and mean left ventricular aortic pressure gradient increased on exercise in all patients. The increase in pressure gradient was less than expected for the concomitant increase in cardiac output so that calculated aortic valve area increased on exercise in comparison to the resting value. This observation has previously been documented by Bache and associates<sup>2</sup> and is due either to an alteration in valve configuration with an actual increase in valve area on exercise or to a commissural artifact.

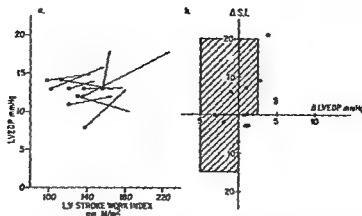


Fig 7 = Change in preoperative left ventricular end-diastolic pressure (LVEDP) relative to change in left ventricular (LV) stroke work index on exercise. The direction of change is indicated by the arrow. b Preoperative (closed circle) and postoperative (open circle) change in left ventricular stroke index (SL) on exercise relative to change in LVEDP. The shaded area represents the normal response.

The increase in cardiac output produced by supine leg exercise was mainly the result of an increase in heart rate. The stroke volume changed little. In some patients there was a decrease in stroke index in spite of an increase in LVEDP suggesting decreased myocardial function. If the change in stroke work index on exercise is compared to the change in LVEDP on exercise then all the children showed a normal response with a major increase of stroke work index associated with only a slight increase or no change in the LVEDP. This is in sharp contrast to exercise studies done in adults with severe aortic stenosis where many patients showed an actual decrease or little change in SWI in spite of a major increase in LVEDP on exercise and suggests more severe myocardial dysfunction in adults with aortic stenosis. There were several possible explanations for this:

- 1 Aortic stenosis becomes increasingly severe with age, particularly with calcification of the aortic valve in older adults.

- 2 Long-standing myocardial hypertrophy results in increased myocardial dysfunction.

- 3 Myocardial ischemia related to decreased coronary perfusion in the face of increased demand and complicated by coronary atherosclerosis.

Probably all three factors contribute to increased myocardial dysfunction with age.

The postoperative exercise studies in our patients show a significant improvement compared to the preoperative exercise hemodynamics. The peak left ventricular pressure and mean left ventricular aortic pressure gradient on exercise are significantly decreased by successful surgery.

Some patients in this study still showed a decrease in stroke volume on exercise in spite of an increasing LVEDP. In most this may be artifact since they had aortic insufficiency and the Fick stroke volume underestimates the true forward stroke volume. In one patient however there was no aortic insufficiency and so this explanation does not apply and he clearly still has evidence for ventricular dysfunction. In previous pre and postoperative rest and exercise hemodynamic studies in patients with pulmonary stenosis who had a pulmonary valvotomy all the postoperative patients showed a normal relationship between the stroke index and RVEDP on exercise in contrast to a high percentage which had shown an abnormal response before surgery. Pulmonary valvotomy is more effective in reducing right ventricular systolic pressure and right ventricular pulmonary artery pressure gradient at both rest and exercise and resulted in a significant decrease in the right ventricular end-diastolic pressure at rest and exercise after surgery. This probably reflects a reduction in the degree of right ventricular hypertrophy and reflects better results from pulmonary valvotomy. Also pulmonary insufficiency is relatively unimportant and this permits the surgeon to be more vigorous in his attempts to open the valve accounting for the better result.

The role of aortic stenosis in producing subendocardial ischemia in children and adults has received considerable attention recently.

The papillary muscle infarction seen in some young infants with severe congenital aortic stenosis represents an extreme example of subendocardial ischemia. The ST segment depression

sion which may be present at rest or can be produced by exercise in some children with moderately severe or severe aortic stenosis probably reflects the myocardial ischemia induced by an increased work load.<sup>1</sup>

The  $DPTI \times O / SPTI$  ratio has been shown experimentally to correlate with other methods of estimating subendocardial blood flow. A ratio of less than 10 was regarded by Lewis and associates as indicating subendocardial ischemia and was common in their patients who had severe valvar aortic stenosis (aortic valve area less than  $0.7 \text{ cm}^2/\text{M}^2$ ). Forty-four % of our patients had a resting value of less than 6 at rest preoperatively. This patient was three months old and had a calculated aortic valve area of less than  $0.36 \text{ cm}^2/\text{M}^2$  and a heart rate of greater than 180. The combination of severe aortic stenosis with a low aortic valve area and a high heart rate results in a low ratio. Twelve of 80 patients studied by Lewis and co-workers had ratios less than 6; all had an aortic valve area of less than  $0.45 \text{ cm}^2/\text{M}^2$  or heart rates above 120. Eight of the 12 were less than one year of age. Subendocardial ischemia is therefore a greater problem in infants with severe stenosis and contributes to the poor prognosis in patients with severe aortic stenosis in infancy.

Exercise results in an increase in the systolic pressure and heart rate and a decrease in diastolic filling time. Thus it is not surprising that each of our patients with severe aortic stenosis showed a major decrease in  $DPTI \times O / SPTI$  with exercise. In all patients the ratio dropped to less than 10 and in three patients to less than 6. Successful aortic valvotomy resulted in a significant improvement in this ratio both at rest and on exercise reflecting improved myocardial perfusion.

The postoperative rest and exercise hemodynamics including the indirect assessment of subendocardial ischemia using the  $DPTI \times O / SPTI$  ratio are not only useful in assessing the results of surgery but also in determining the advisability of normal exercise activity after valvotomy. Those patients with only minor residual gradients or minimal aortic insufficiency

normal exercise response and normal  $DPTI \times O / SPTI$  ratios at rest and exercise can probably be permitted normal exercise activity. Restrictions placed on other patients would depend upon the degree of residual abnormalities at rest and exercise.

### Summary

The rest and exercise hemodynamics in children with congenital valvar aortic stenosis were studied before and after aortic valvotomy. Eighteen patients were studied at rest; ten of the 18 patients were also studied during supine leg exercise using a bicycle ergometer.

Aortic valvotomy resulted in a significant reduction in the mean left ventricular aortic pressure gradient and in peak left ventricular systolic pressure with an increase in aortic valve area in most patients. There was an associated increase in the subendocardial blood flow assessed indirectly by the  $DPTI \times O / SPTI$  ratio. There was a minor increase in the degree of aortic insufficiency in most patients.

Although in general there was significant hemodynamic improvement, three of the 18 patients still had significant residual stenosis after surgery and another four patients had a major increase in aortic insufficiency. The three patients with residual obstruction and one of the four patients with moderate to severe aortic insufficiency still had a  $DPTI \times O / SPTI$  ratio of less than 10, suggesting possible residual subendocardial ischemia. Also, the increased left ventricular end-diastolic pressures (LVEDP) present in nearly 50% of the patients before surgery did not change significantly after surgery. Three patients showed an actual increase in LVEDP after surgery.

Before surgery, the left ventricular systolic pressure and mean gradient increased on exercise but this increase was proportionately less than the increase in cardiac output so that calculated aortic valve area increased on exercise. The  $DPTI \times O / SPTI$  ratio decreased significantly on exercise, suggesting an increase in myocardial ischemia. Successful surgery resulted in a reduction in left ventricular systolic pressure and mean left ventricular aortic gradient on exercise and in improvement in the subendocardial blood flow as assessed by the  $DPTI \times O / SPTI$  ratio.

In general, children with severe aortic stenosis have relatively normal cardiac function at rest. Some children did show a reductio

index on exercise in spite of rising LVEDP. However stroke work index increased in all of our children. Adult studies have shown many patients with decrease in stroke work index relative to LVEDP on exercise.

The results of pre and postoperative rest and exercise hemodynamics may be useful in evaluating results of surgery. The postoperative hemodynamic evaluation including the use of  $DPTI \times O_2 / SPTI$  ratio provides additional useful information which can be used in making decisions concerning exercise activity after surgery.

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## Exercise-induced ventricular ectopy in children and young adults with complete heart block

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The response of patients with non-ischemic complete heart block (CHB) to exercise has long been of interest to cardiologists. Most investigators have focused on the heart rate response and on the compensatory changes that enable these patients to maintain a cardiac output appropriate to their activity despite the often profound bradycardia. Some have noted the appearance of ventricular ectopic activity (VEA) during strenuous exercise—even in the absence of associated structural heart disease. The purpose of this study was to investigate the frequency and severity of exercise elicited ventricular ectopy in young people with non-ischemic heart block and to attempt to interpret its clinical significance.

### Subjects and methods

**CHB subjects** The study group (Table I) consisted of 25 children and young adults aged 3 to 29 years (median age 17 years) with complete atrioventricular block. Patients who were acutely ill, those with transient block, or cardiac pacemakers and those receiving cardiac medications were excluded from this study. There were 17 males and eight females. Fourteen of the patients had isolated or congenital block with no associated structural defects and no history of illness predisposing to acquired block. Seven patients with

block had associated cardiac defects; six of these had L-transposition of the great arteries complexes (L-TGA) (congenitally corrected transposition). Four patients had surgically acquired block following repair of assorted congenital defects.

**Control subjects** The control group was made up of 50 children and young adults without heart disease who were referred for exercise testing for evaluation of atypical chest pain, poor exercise tolerance, hypertension, or syncope. None of these patients had significant heart disease on the basis of physical examination, electrocardiogram (ECG), and in most cases chest x-ray. Those who were referred for evaluation for possible arrhythmia (e.g., history of palpitations, conduction abnormalities on resting ECG) were excluded as were those receiving cardiac medication.

**Procedure** Each subject underwent a graded maximal exercise test on the treadmill with the speed and grade of the treadmill increased every three minutes according to the Bruce protocol. Leads II, aV<sub>F</sub>, and a modified V<sub>5</sub> were monitored continuously starting three minutes prior to exercise and extending through ten minutes of recovery and were recorded photographically on a Sanborn Polybeam recorder with simultaneous magnetic tape recording system for playback where desired. Exercise was terminated when the subject reached the limit of his or her tolerance. Only those who exercised past their anaerobic threshold, verified by venous serum lactate levels of 60 mEq/L or greater at one minute of recovery, were included.

**Analysis of data** All exercise test tracings were reviewed for presence, degree, and frequency of

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Table I Summary of data on 25 patients with complete heart block

	Case No	Sex	Age (yrs)	Defects	QRS duration (sec)	Heart rate		Endurance time Bruce protocol (min)	Exercise tolerance (mile)	Ectopys ore	
						Rest	Exercise			Rest	Exercise
Group 1											
Congenital											
	1	F	17	None	0.04	4	120	10	0	1	3
	2	M	24	None	0.08	52	10	11	10	0	4
	3	F	19	None	0.06	39	10	12.8	>90	0	4
	4	M	17	None	0.08	55	146	13	50	0	3
	5	M	24	None	0.12	43	76	13.2	50	0	0
	6	M	7	None	0.08	48	9	12.0	50	0	0
	7	M	24	None	0.09	44	70	9.5	<5	0	3
	8	F	21	None	0.09	43	82	9.1	25	0	0
	9	M	16	None	0.09	50	100	17.3	>90	0	0
	10	F	14	None	0.04	60	126	11.3	0	0	9
	11	F	13	None	0.11	40	109	12.4	50	0	3
	12	M	4	None	0.12	47	51	6	10	0	0
	13	F	13	None	0.08	50	103	13.7	75	0	2
	14	F	21	None	0.07	36	105	9.8	25	0	3
Group 2											
Associated defects											
	15	M	14	L-TGA	0.11	80	129	13.3	20	2	4
	16	M	20	MR	0.06	42	120	16.3	>90	0	2
	17	M	5	L-TGA	0.10	57	68	6.8	10	0	0
	18 †	M	20	L-TGA	0.14	53	68	6	<5	1	5
	19	M	29	L-TGA	0.10	63	96	8.5	<5	1	5
	20	M	24	L-TGA	0.07	73	90	9.6	<5	0	0
	21 †	M	27	L-TGA	0.16	63	97	7.0	<5	0	4
Group 3											
Surgical											
	22	F	23	TOF	0.14	38	67	7.2	<5	0	5
	23	M	10	D-TGA	0.08	47	118	13.8	0	0	0
	24 †	M	21	ASD I	0.14	73	170	8.3	<5	3	5
	25	M	15	MR TAPVR	0.06	63	81	11.4	10	0	0

† Inequivalently corrected congenital.

‡ Died.

§ See Table II.

Abbreviations: TGA = transposition of the great arteries; MR = mitral regurgitation; TOF = tetralogy of Fallot; ASD I = atrial septal defect, primum; TAPVR = total anomalous pulmonary connection.

ventricular ectopy grading the ectopic activity by a modification of the system suggested by Lown and Wolf (Table II). Each subject was assigned a resting score and exercise score. The former was the highest grade of ectopy seen on either the routine ECGs for the year preceding the test or during the control period before the exercise test. The latter was the highest grade of ectopy seen during exercise or early in the recovery period. Exercise tolerance expressed in percentile for age and sex is derived from a comparison of duration of maximal exercise with data from normal untrained subjects.

The Kolmogorov-Smirnov test for the deviation between two sample cumulatives was used for analysis of the severity of ectopy (according to the Lown and Wolf criteria) and the chi-square test was employed for analysis of its frequency. Linear regression was used to evaluate the relationship between heart rate and both age and severity of ectopy.

## Results

Background data and the results of exercise testing are summarized in Table I. Grade I ectopy occurred at rest in three of 25 (12%) CHB subjects

Table II Grading of ventricular ectopy

0	No ectopy
1	Unifocal PVC <1/minute
2	Unifocal PVC >1/minute
3	Multifocal PVC
4	Couplets (paired PVC)
5	Ventricular tachycardia

Abbreviations: PVC = premature ventricular contractions

and none out of 50 of the controls ( $p > 0.05$ ). No Grade 1 ectopy was induced by exercise in either group. The frequency of significant ectopy (Grade 2 or higher) at rest and at exercise in the subjects with heart block and the controls is illustrated in Fig 1. At rest there was no significant difference with regard to the frequency of significant ectopy: none out of 50 in the control group and two of 25 (8%) in the heart block group ( $p = > 0.10$ ). At exercise, however, significant ectopy was present in 68% (17 of 25) of patients with heart block but only 2% (one of 50) of the controls (a girl with a single couplet) ( $p = < 0.01$ ). Of the 17 patients with heart block who developed ectopy, complex forms (Grade 3, 4, or 5) were present in 82% (14 of 17). The heart block patients showed a significantly higher grade of ventricular ectopy than the controls ( $p = < 0.01$ ). The three groups (those with isolated congenital block, those with block and associated lesions, and those with surgically induced heart block) did not differ significantly either in frequency or severity of ventricular ectopy on exercise ( $p = > 0.10$ ). The appearance of ventricular ectopy was age related: no ectopy was induced in children under ten years of age and the most advanced forms were induced in the patients over 20 years of age (Fig 2). This trend toward increasing frequency and severity of ventricular ectopic activity with age is significant at the 0.05 level.

There was no appreciable correlation between age and resting ventricular rate ( $r = 0.4$ ) or between age and maximum ventricular rate achieved with exercise ( $r = 0.3$ ), nor was resting heart rate correlated with ventricular ectopy on exercise ( $r = 0.6$ ). The proportion of patients with ectopy increased with increasing maximum heart rate but not significantly ( $p = 0.16$ ), and the scatter of the data was such that they were consistent also with a weak trend in the opposite direction that is for increasing ectopy with decreasing maximum rate.

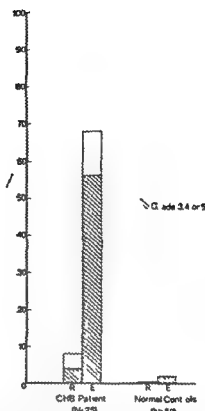


Fig 1 Frequency of significant ventricular ectopy (Grade 2 or higher) at rest (R) and with exercise (E) in 25 patients with complete heart block (CHB) and in 50 control subjects.

Patients with QRS duration greater than two standard deviations above the mean for age<sup>1</sup> on the resting electrocardiogram were compared with the remainder of the heart block patients (Fig 3). Those with prolongation showed a greater frequency of very severe (Grade 3, 4, or 5) ectopy with exercise ( $p = < 0.05$ ) than did those with a normal QRS duration.

No significant difference was seen between the girls and the boys in either frequency or severity of ectopy induced.

Exercise tolerance was diminished (greater than two standard deviations below the mean for age and sex) in seven of 25 (28%) of the patients with heart block (one of 14 (8%) with congenital block, four of seven (57%) with associated lesions, and two of four (50%) with surgically induced block). Normal tolerance occurred significantly more frequently in the congenital CHB patients than in the remainder of the subjects ( $p = < 0.01$ ). The subjects with diminished tolerance did not differ significantly from those with normal tolerance in either frequency ( $p = > 0.10$ ).



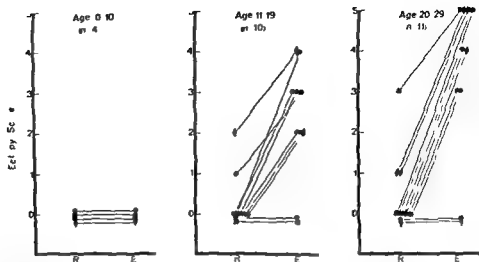


Fig 2 Age distribution of ventricular ectopy at rest (R) and with exercise (E) in 25 patients with complete heart block. Symbols: ● congenital block ▲ associated cardiac defects ■ surgical block.

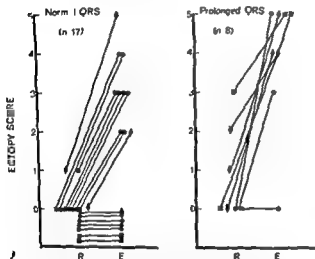


Fig 3 Ventricular ectopy score at rest (R) and with exercise (E) in 17 CHB patients with normal QRS duration and in eight patients with prolonged QRS. Symbols same as in Fig 2.

or severity ( $p = >0.05$ ) of ventricular ectopy at rest or with exercise; no significant difference in age ( $p = >0.10$ ) or QRS duration ( $p = >0.10$ ) was found between these two groups.

Clinical follow up of the patients for up to 36 months since exercise study reveals 19 who are asymptomatic on no cardiac medications. The remaining six have undergone implantation of permanent demand mode pacemakers: two for Adams Stokes attacks and two for maintenance of ventricular rate during pharmacological suppression of ventricular ectopy; and in two concurrently with intracardiac repair or complex congenital heart disease. Four of these patients

were placed on antiarrhythmic medications.

There have been three sudden deaths (Cases No 18, 21, and 24). These patients were over 20 years of age, had associated cardiac disease and had shown Grade 4 or 5 ventricular ectopy activity on exercise. All three had high grade ventricular ectopy at rest after the placement of functioning pacemakers and the administration of antiarrhythmic agents. Repeat exercise testing after pacemaker insertion had not been performed.

## Discussion

We found ventricular ectopy to occur frequently with exercise in children and young adults with complete heart block. Although this phenomenon has been noted previously, it has not been systematically examined in a sizable series. Of the reported cases of children with heart block in whom the presence or absence of ventricular ectopy on exercise is mentioned, it was elicited in 39% (24 of 61).<sup>11</sup> Our incidence was somewhat higher possibly because our protocol required maximal exercise, which has been shown to be more sensitive in elicitation of ventricular ectopy than submaximal exercise.<sup>12</sup>

The prognostic significance of ventricular ectopy is not clear. Several studies in normal adults and in adults with coronary heart disease have shown a higher risk of sudden death in those with ectopy, especially with high grades of ectopy.<sup>13</sup> Children with isolated congenital block are also at risk for sudden death. Although such deaths were originally attributed to bradycardia,<sup>14</sup> children

children like their adult counterparts<sup>14, 15</sup> may have Adams Stokes attacks in some cases fatal due to ventricular tachycardia or fibrillation.<sup>16</sup> The presence of severe ectopy at rest or at exercise may help to identify the child at risk. An artificial pacemaker may not completely protect the heart block patient from this type of Adams Stokes attack as was unfortunately demonstrated in three of our patients.

No difference was found in our study in the incidence or severity of ectopy between those patients with isolated congenital block, those with surgical block and those with associated structural defects. This was somewhat unexpected in light of the reported association of surgically acquired block with a high risk of sudden death<sup>1</sup> contrasted to the more benign prognosis<sup>17</sup> of isolated congenital block. Our sample of patients with surgical block is a small one however and biased toward the most stable since the large majority of children with surgically acquired heart block in our institution receive pacemakers early and hence were not eligible for this study. No deaths have as yet occurred among the 14 isolated heart block patients including those with high grade ectopy on exercise suggesting that the overall risk for sudden death in CHB may be higher in those with associated heart disease reflecting other factors such as congestive failure or hypovolemia in addition to the presence and severity of ectopy.

Ventricular ectopy was more likely to occur and was more severe among older patients independent of QRS duration. Although longitudinal data on ectopy in patients with complete heart block are not yet available, this age relationship raises the possibility that heart block even in its isolated congenital form may be a progressive disease. The tendency to more severe forms of ectopy in subjects with QRS prolongation is not unexpected; such patients are known to be at increased risk of syncope and sudden death. In fact, in the first description of Adams Stokes attacks in children with congenital complete heart block reported by Moithan and associates in 1962, QRS prolongation was present in the two documented cases in which ventricular ectopy initiated the attacks. A more detailed analysis of the contribution of the level of block would require electrophysiologic studies which were not available in a majority of our subjects.

Exercise tolerance was normal in our patients

with isolated congenital heart block but was significantly limited in some with associated heart defects or surgically acquired block as has been shown by other investigators.<sup>18</sup> Ventricular ectopy was not related to tolerance and many patients developed the worst arrhythmias during the recovery period supporting the concept that ectopy occurs in response to stress relative to the individual rather than to the predicted norm.

The etiology of ectopy in complete A V block remains unknown. That it occurs purely as a reflection of low ventricular rate is unlikely in light of the low incidence of ectopy at rest. The absence of a significant trend toward increased ectopy on exercise with lower heart rates is in agreement with the data of Ikhs and Hanson.<sup>1</sup> We were unable to substantiate the assertion of Chawla and co-workers that the elicitation of ventricular ectopic activity was associated with inadequate chronotropic effect. Our data support the premise of Levy and colleagues<sup>19</sup> that CHB is a complex disease rather than a simple problem of low heart rate. However, the small number of patients previously reported<sup>1</sup> and those added here<sup>20</sup> insufficient to answer this question definitively.

We have demonstrated a tendency toward ventricular ectopy on exercise in children and young adults with complete heart block. We believe that there may be an increased risk for sudden death in those patients with ectopy especially in the older patients with associated cardiac abnormalities and that pacemakers may not necessarily be protective.

### Summary

Twenty-five children and young adults with complete heart block and 50 normal control subjects were maximally exercised on a treadmill and their electrocardiograms were analyzed for the presence and degree of ventricular ectopy activity. Sixty-eight % (17 of 25) of the heart block patients had significant ventricular ectopy (frequent unifocal ectopy or worse) on exercise compared to 2% (one of 50) of the controls ( $p = <0.01$ ). In the patients with block there was a significant trend toward more frequent and more severe ectopy with increasing age ( $p = <0.05$ ) independent of heart rate.

More severe ventricular ectopy was also seen in those patients with QRS prolongation ( $p = <0.05$ ). No significant differences were

found between the 14 patients with isolated congenital heart block the seven with associated defects and the four with surgically acquired block. We believe that severe ventricular ectopy is common at exercise in patients with complete heart block and they may have an increased risk for sudden death.

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## Case reports

### Echocardiographic detection of a retained left atrial catheter

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Echocardiography has become an established diagnostic tool in the evaluation of patients who have recently undergone open heart surgery. Extensive experience has now been gained with the use of this diagnostic method in the detection of postoperative pericardial effusion.<sup>1-3</sup> Echocardiographically demonstrable changes in segmental left ventricular function following coronary or valvular surgery have been described.<sup>4-6</sup> The function of valve prostheses in the early postoperative period has also been studied through this noninvasive means.<sup>7</sup>

We have recently used M Mode echocardiography to detect a retained left atrial catheter in a patient with unusual neurologic signs following open heart surgery. Documentation of the presence of the catheter within the left atrium led to reoperation and removal of the foreign body.

#### Case report

An 18-year-old woman was admitted with congestive heart failure resulting from penetrating chest trauma. She underwent the surgical repair of mitral and tricuspid valve lacera-tions and closure of a traumatic interventricular septal defect. A left atrial catheter (B D Vinyl Marked Tubing No. 6118) was implanted at the time of operation in order to facilitate hemodynamic monitoring in the postoperative period. On the fifth postoperative day the left atrial catheter was noted to be non functional and was presumed to be occluded by thrombus. An attempt to remove it completely in the bedside was unsuccessful, but it was felt by the surgeon that the line had been withdrawn sufficiently so that the entire catheter was

extra-cardiac. A routine chest x ray failed to demonstrate the position of the catheter; in fact no portion of the catheter could be seen on the chest film.

Five days later the patient developed transient left homonymous hemianopsia which was thought most likely due to a cerebral embolism. Anticoagulation therapy was begun. An echocardiogram (Fig 1) showed a markedly dense linear echo within the left atrium. The diagnosis of intra atrial catheter retention was made and complete removal of the left atrial catheter was performed via thoracotomy under general anesthesia. At surgery the proximal end of the catheter was located in the pericardial space held only by an anchoring suture on the lateral pericardium. The catheter was withdrawn from its insertion site in a superior pulmonary vein without difficulty and the left atrium was not re-opened. Thrombus filled the distal lumen of the catheter.

Subsequently the patient did well without any further embolic episodes. An echocardiogram was repeated (Fig 2) and the dense echo band was no longer present in the left atrium.

The patient has been free of symptoms during the 15 months since the removal of the left atrial catheter.

#### Discussion

The presence of catheters within cardiac chambers is usually detectable echocardiographically. Since they are foreign bodies of considerable width Swan Ganz catheters reflect ultrasound strongly and have within the heart characteristic motion patterns which have been well described.<sup>8-11</sup> During routine cardiac catheterization it is possible to follow the motion pattern of intracardiac catheters as they traverse the chambers on both sides of the heart. However there have been no previous reports of the echocardiographic appearance of cardiac catheters in the left atrium either at the time of cardiac catheterization or following cardiac surgery.

In our patient the demonstration of a catheter in a left heart chamber had great the

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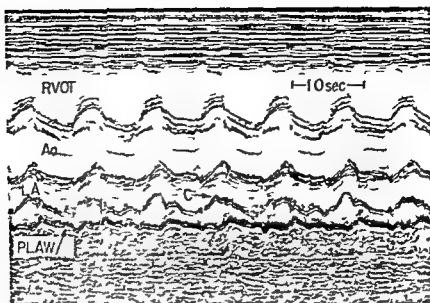


Fig 1 Echocardiogram before the removal of the intra atrial catheter. The catheter (C) is visualized as a markedly dense linear echo within the left atrium. RVOT = right ventricular outflow tract. Ao = aortic root. LA = left atrium. PLAW = posterior left atrial wall.

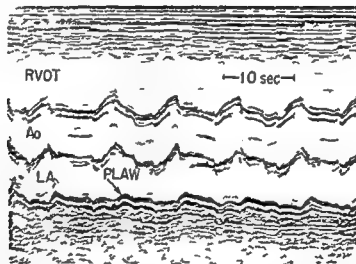


Fig 2 Echocardiogram after the removal of the intra atrial catheter. The linear band is no longer seen within the left atrium. RVOT = right ventricular outflow tract. Ao = aortic root. LA = left atrium. PLAW = posterior left atrial wall.

implications. The catheter had become non functional several days following surgery. In our experience this problem has always been due to occlusion of the line by thrombus and we always advise removal of such lines as soon as the left atrial pressure is damped. However, in this case, normal traction upon the external portion of the catheter failed to dislodge it from the chest completely. Nevertheless, the surgeon performing the procedure felt that the catheter had been removed from the heart. Examination of the

routine chest x ray was not helpful since the catheter could not be located on the film. Echo demonstration of the intracavitary position of the catheter was followed promptly by return of the patient to the operating room for complete removal of the device. The echo free appearance of the left atrium following this procedure confirmed the impression that the echo dense linear band had been due to the catheter.

We have presumed that her neurologic syndrome preceding final removal of the catheter

was due to systemic embolization from the catheter tip while it was still within the left atrium. Inspection of the catheter after its removal from the left atrium did demonstrate extensive fibrin thrombus in its distal lumen. The left atrium itself was not re-explored since the catheter was easily withdrawn from the superior pulmonary vein. Therefore we cannot fully exclude the possibility that mural thrombus elsewhere in the atrium was also a potential source of cerebral embolization. However, no detectable embolization occurred after removal of the catheter.

Left atrial catheter retention with subsequent systemic embolization is a potential complication of this form of postoperative hemodynamic management. In fact, many now favor the preoperative placement of Swan-Ganz pulmonary artery lines for the indirect measurement of left heart filling pressure.

We would recommend that if a left atrial catheter is used, an echocardiogram be performed preoperatively and in the early postoperative period. In this way the baseline appearance of the left atrium and the echo characteristics of the intra-atrial catheter can be established. We have been unable to determine the position of these faintly radiopaque catheters on chest x-rays done in the postoperative period and do not recommend reliance on chest roentgenography in these cases.

If an attempt to remove a left atrial catheter is unsuccessful, an echo study should be repeated to inspect the left atrium for signs of retention of the line. From our experience, these catheters are remarkably echo-dense in spite of their narrow diameters. Demonstration of this foreign body within the left atrium would justify, and indeed make mandatory, repeat thoracotomy for removal of the catheter.

Although M-Mode echocardiography easily demonstrates the presence and location of intra-cardiac catheters, it is anticipated that two-dimensional sector scanning will be used to provide even more detailed pictures of these foreign bodies in the future.

## Summary

An 18-year-old woman underwent the repair of traumatic lacerations of the mitral valve, tricuspid valve, and interventricular septum. At the time of surgery, an indwelling left atrial catheter was placed for postoperative hemodynamic management. An attempt to remove the catheter completely several days following surgery was unsuccessful, but it was initially assumed by the surgeon that the tip of the catheter had been withdrawn from the left atrium. When the patient developed neurologic signs suggesting a cerebral embolism, an echocardiogram was performed. Echo demonstration of the catheter in the left atrium led to repeat thoracotomy for removal of the retained line.

Baseline echocardiograms are indicated in cardiac surgical patients with indwelling left atrial catheters, and echo study can be diagnostic if catheter retention occurs.

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# Morbidity associated with anomalous origin of the right coronary artery from the left sinus of Valsalva

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Anomalous origin of the right coronary artery from the left sinus of Valsalva is considered benign clinical sequelae have generally been related only to the coexistence of atherosclerosis.<sup>1</sup> Selective catheterization of the anomalous artery has been reported in two patients with angina like chest pain but no abnormalities other than the anomalous origin were noted.<sup>2</sup> A recent review of coronary anomalies notes that the "hemodynamic significance has not yet been firmly established in right coronary origin from the left sinus of Valsalva." The case that follows suggests that this anomaly even without atherosclerosis may be associated with significant cardiovascular morbidity and that compression of the early portion of the artery may be responsible

## Case report

A 41-year-old man had a five minute episode of anterior chest pain followed two days later by several syncopal episodes. On admission to another hospital he was noted to have second-degree A-V block which progressed to third degree A-V block requiring a permanent pacemaker. The ECG showed marked T wave inversion in inferior and lateral precordial leads (Fig 1). Serum levels of cardiac enzymes were normal.

He was referred to the Veterans Administration Hospital in Iowa City, Iowa, for evaluation of the heart block. He had felt well except for an occasional chest pain of short duration at rest. On physical examination BP was 110/70 mm Hg, pulse

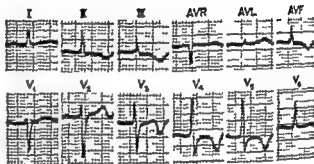


Fig 1 Electrocardiogram at initial hospitalization.

at rest was 72 beats per minute and regular. With walking the pulse increased to 111 beats per minute. There was a pulse generator in the right infraclavicular region. Cardiac examination revealed a normal S<sub>1</sub>, normal S<sub>2</sub>, and an S<sub>3</sub> gallop. Remainder of the examination was unremarkable. The ECG showed a ventricular pacemaker firing at "3 beats per minute with 100% capture." A chest x-ray showed the permanent transvenous pacemaker in the right ventricular apex. A thallium scan with exercise revealed hypoperfusion of apical and posterior septal regions. Delayed views were not obtained.

Cardiac catheterization was performed to determine the etiology and location of the conduction system disease. Electrophysiologic studies revealed sinus rhythm at a rate of 77 beats per minute. Second-degree A-V block with Wenckebach phenomenon occurred with an atrial pacing rate of 81 beats per minute. Following 1 mg of intravenous atropine sulfate, second-degree A-V block with the Wenckebach phenomenon occurred at an atrial pacing rate of 155 beats per minute. H-V intervals at all levels of atrial pacing before and after atropine were normal. The left ventriculogram showed an ejection fraction of 38% with apical hypokinesis and posterior wall dyskinesis. Retrograde femoral coronary arteriograms revealed a normal, nondominant left coronary artery. The right coronary artery could not be selectively catheterized in spite of multiple attempts with a variety of catheters. On aortic root injection the right coronary artery was seen to originate from the left sinus of Valsalva and crossed the aortic root

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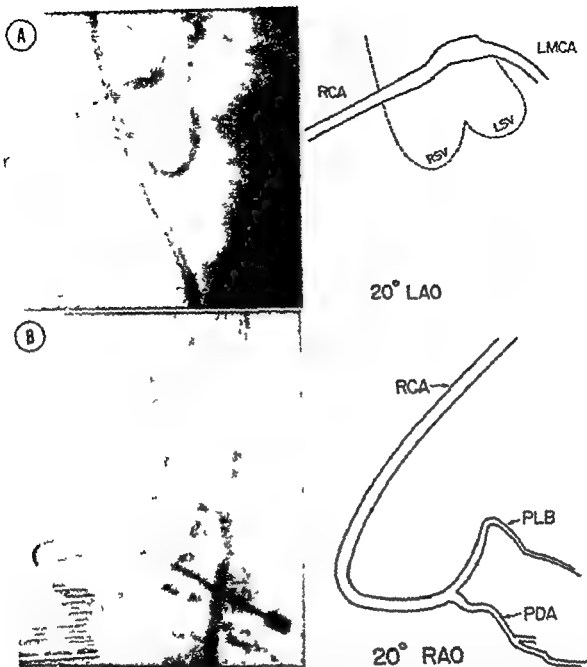


Fig 2 Coronary arteriograms and corresponding drawings of the anomalous right coronary artery in the patient discussed. A 20 degree LAO projection. B 20 degree RAO projection. Note the proximity of the right and left coronary artery ostia (A permanent pacemaker catheter is present). LMCA = left main coronary artery. PDA = posterior descending artery. PLB = posterolateral branch of the right coronary artery.

anteriorly, but was not outlined sufficiently for detailed analysis.

On the patient's return to the catheterization laboratory, selective catheterization of the anomalous right coronary artery was obtained using a No 1 left Amplatz coronary catheter with a Seldinger femoral artery approach. A dominant, nondiseased right coronary artery arising from the left sinus of Valsalva was demonstrated (Fig 2). The A nodal artery arose from the anomalous right coronary artery. The

first portion of the anomalous artery could be seen to be transiently narrowed by 20% during systole (Fig 3).

#### Discussion

The patient described here had significant morbidity associated with anomalous origin of the right coronary artery from the left sinus of Valsalva. Dyskinesis of the left ventricular wall in



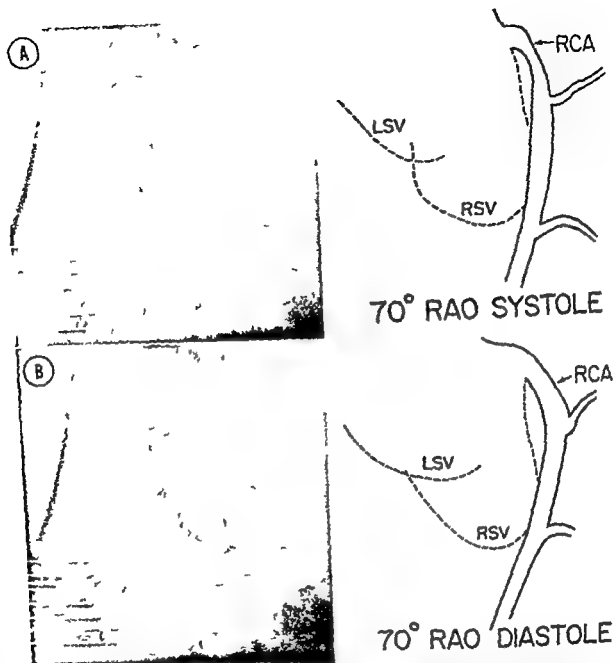


Fig 3 Forty five degree RAO coronary arteriograms with corresponding drawings of the anomalous right coronary artery in the patient during A systole and B diastole Note the narrowing during systole Simultaneous electrocardiogram is in the left lower corner of each frame

the distribution of a nondiseased anomalous right coronary artery occurred in a 25 year old man. Selective angiographic demonstration of the anomalous artery was essential to determine the presence or absence of luminal narrowing in the anomalous artery.

Anomalous origin of the coronary arteries has been reviewed by many authors. The incidence of all coronary anomalies ranges from 0.5% to 1.2%, and anomalous origin of the right coronary artery from the left sinus of Valsalva is

reported to constitute from 6% to 27% of all coronary anomalies.<sup>3, 10</sup>

There is apparently no relationship between the type of anomaly and the presence or degree of coronary sclerosis. Moreover, there is no preselection for atherosclerosis in anomalous coronary arteries.<sup>1, 11</sup> Liberson and associates<sup>2</sup> reported four patients with coronary atherosclerosis and anomalous origin of the right coronary artery from the left sinus of Valsalva. None had atherosclerosis in the anomalous artery.<sup>2</sup>

The consensus has been that anomalous origin of the right coronary artery in the absence of arteriosclerotic lesions is benign.<sup>1,3,10,11</sup> Thompson and colleagues<sup>1</sup> reported two cases with probable angina and Chaitlin and co-workers<sup>3</sup> briefly mention a 30 year old man with a nondiseased anomalous right coronary artery who had evidence of an inferior myocardial infarction by ECG and enzymes. The case presented here is the first detailed report in which anomalous origin of the right coronary artery from the left sinus of Valsalva was associated with significant morbidity in the absence of an associated atherosclerotic lesion.

How could morbidity occur with this anomaly in the absence of atherosclerosis? In patients where an anomalous main left coronary artery originates from the right sinus of Valsalva and courses between the aorta and pulmonary artery, significant morbidity and mortality occur.<sup>1,11</sup> Atherosclerosis is not found in most patients who die from this anomaly. The etiology of this phenomenon is not known but two major explanations have been proposed. First the aorta and pulmonary artery might expand sufficiently with exercise to compress the coronary vessel passing between them. Patients have been described in whom myocardial infarction has occurred when a nonatherosclerotic left coronary artery with anomalous origin follows a course anterior to the pulmonary artery or posterior to the aortic root and therefore could not be compressed between the great vessels. This fact suggests that other mechanisms may also be responsible for morbidity in patients with anomalous aortic origin of the coronary arteries.

Closure of the anomalous ostium within the aortic wall may be a more tenable mechanism for infarction and sudden death.<sup>6</sup> With expansion of the aorta during the systolic pressure rise with exercise or hypertension a slit like arterial segment coursing tangentially through the aortic wall could easily be narrowed or occluded. Systolic compression of the anomalous artery appeared to occur in our patient with a nondiseased anomalous right coronary artery but was not severe at rest as judged by the extent of narrowing seen (Fig. 3). Either or both of these mechanisms might have been responsible for the morbidity reported herein.

While sudden death has not been reported with anomalous right coronary artery from the left

sinus of Valsalva this anomaly does appear to produce morbidity independent of atherosclerotic sequelae and may not be a totally benign lesion. Selective demonstration of the anomalous right coronary artery is necessary to diagnose correctly and treat patients with chest pain and this anomaly. In the absence of atherosclerosis surgical revision of an anomalous aortic origin of a coronary artery has been performed in one patient with anomalous left main coronary artery from the right sinus of Valsalva which had been associated with syncope and cardiac arrest. Whether surgical revision might be beneficial in a patient with anomalous right coronary origin from the left sinus of Valsalva remains to be demonstrated.

### Summary

Anomalies of the coronary arteries occur infrequently but can have major clinical consequences. Many reports have described an association between sudden death and origin of the left coronary artery from the right sinus of Valsalva but origin of the right coronary artery from the left sinus of Valsalva is thought to be benign. Herein we describe a patient in whom anomalous origin of the right coronary artery from the left sinus of Valsalva was associated with significant cardiovascular morbidity. A 25 year old man developed complete heart block and myocardial infarction in the distribution of a dominant anomalous right coronary artery free of atherosclerotic lesions. Systolic compression at the origin of the anomalous artery was demonstrated. The left coronary artery was normal. We conclude that anomalous origin of the right coronary artery from the left sinus of Valsalva may be associated with significant cardiovascular morbidity in the absence of atherosclerosis.

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## Current concepts of left ventricular relaxation and compliance

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Cardiac relaxation is impaired in many cardiac disorders and is the subject of extensive investigation. As ventricular relaxation proceeds during diastole the heart fills with a given stroke volume and it is this volume which is ejected during the succeeding systole. Abnormal ventricular relaxation is thus necessarily accompanied by alteration in systolic cardiac performance while the consequences proximal to the abnormal cardiac chamber include elevated venous pressures, venous distension and the clinical signs and symptoms of congestive heart failure.

Relaxation is an active process. At a biochemical level important events occur and there are energy dependent intracellular shifts of  $\text{Ca}^{2+}$  ions. At a mechanical level obstruction to left ventricular inflow produces in the experimental animal a negative ventricular pressure with respect to the atmosphere and the pressure-volume (P-V) curve falls to below the zero pressure line at small ventricular volumes in keeping with the old suction theory of ventricular filling.

This review will consider current concepts of cardiac relaxation, biochemical aspects, aspects of muscle mechanics and problems in the intact heart. It will include a review of methods and techniques for the assessment of left ventricular (LV) relaxation and compliance, abnormalities of relaxation in different cardiac diseases and the significance of abnormalities of compliance in the clinical situation.

### Biochemical aspects

The biochemical mechanism of muscle contraction at sarcomere level is shown diagrammatically in Fig 1. Electrochemical activation of the cell is followed by transfer of  $\text{Ca}^{2+}$  ions into the cell across the cellular membrane from the extracellular space and from the lateral sacs of the sarcoplasmic reticulum (SR). This  $\text{Ca}^{2+}$  flux marks the onset of the contraction process. The  $\text{Ca}^{2+}$  binds to the intracellular proteins troponin, tropomyosin, the contractile proteins actin and myosin, interact and the myofilaments slide on each other to produce sarcomere shortening and generation of tension. The process of shortening is physically the result of cross bridge formation or of electrostatic forces which are generated within the sarcomere. The intracellular  $\text{Ca}^{2+}$  rise precedes the build up of tension\* and declines long before contractile tension declines; it is not certain what sustains the force of contraction thereafter—quick release shortening experiments in the barnacle fiber show that sudden muscle shortening produces a small elevation in the declining  $\text{Ca}^{2+}$  transient but muscle shortening also causes a decrease in the muscle's ability to generate force (deactivation theory). There is clearly a relation between mechanical and biochemical elements and mechanical shortening may be a factor in the initiation of relaxation.

The precise mechanisms involved in relaxation of cardiac muscle are not certain—relaxation seems to be governed by the interaction of an activation controlled and a load controlled decay mechanism, the relative contributions of which differ among different animal species.

The transition from the active to the resting state requires a reduction in cytosolic ionized  $\text{Ca}^{2+}$  concentration and this is achieved by (1) a rapid sequestration of  $\text{Ca}^{2+}$  into the SR, (2) the

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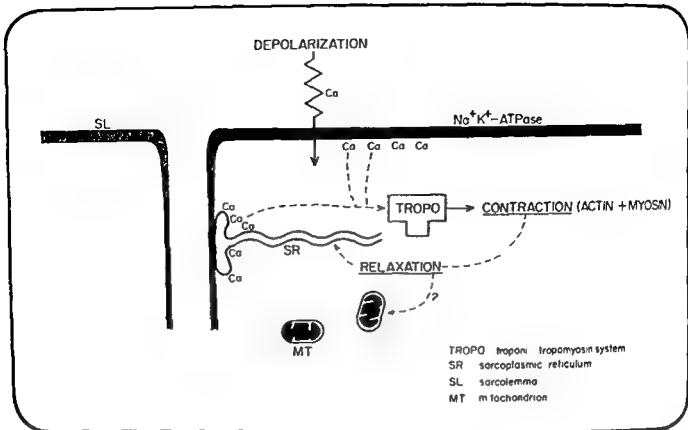
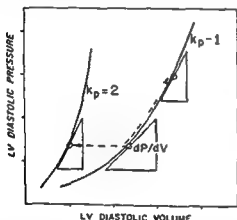


Fig 1 Schematic diagram to show movement of  $\text{Ca}^{2+}$  ions in the cell during contraction and relaxation. Depolarization of the cell is followed by movement of  $\text{Ca}^{2+}$  into the cell, release of  $\text{Ca}^{2+}$  from storage sites and binding of  $\text{Ca}^{2+}$  to troponin leading to contraction. During relaxation  $\text{Ca}^{2+}$  is reuptake by the sarcoplasmic reticulum (SR) and possibly by the mitochondria (MT) removes most of the free  $\text{Ca}^{2+}$  from the cell. (Reproduced from Schwartz A by permission of The Williams & Wilkins Company)



**Fig 2** Diastolic left ventricular pressure-volume (P-V) curves. Chamber stiffness of the ventricle is the change in pressure for a change in volume and measured as a tangent to the P-V curve. As given by  $dP/dV$ . Volume loading of the LV shifts the patient to a steeper part of the P-V curve and  $dP/dV$  (chamber stiffness) increases. The chamber stiffness modulus (slope of the curve) remains  $\approx 1$ . Chamber stiffness ( $dP/dV$ ) also increases if the modulus  $\approx 1$  chamber stiffness increases and the curve becomes more steep (k  $\uparrow$ ). (Reproduced from Gaasch and colleagues by permission of the American Journal of Cardiology.)

return of some  $\text{Ca}^{2+}$  to the extracellular space  
and (3)  $\text{Ca}^{2+}$  buffering mechanisms

1 Accumulation of  $\text{Ca}^{2+}$  by the SR is a rapid energy dependent process energy being derived from the hydrolysis of ATP via a  $\text{Ca}^{2+}$  activated ATPase in the limiting membranes of the SR. Nayler and Williams<sup>2</sup> have suggested that impaired relaxation in heart muscle may theoretically result from an inadequate supply of ATP.  $\text{Ca}^{2+}$  overload failure of the  $\text{Ca}^{2+}$  activated ATPase enzyme leakage of  $\text{Ca}^{2+}$  from the SR or from failure of the cell to return  $\text{Ca}^{2+}$  back into the extracellular phase. There is reversible failure of relaxation (with a resulting rise in resting cardiac tension) in the presence of *hypoxia* where there is deficient mitochondrial function and inadequate ATP substrate to drive the ATPase enzyme of the SR.  $\text{Ca}^{2+}$  reuptake system. Resting muscle tension also increases in *ouabain* contractions due to diminished tissue stores of ATP and a later rise in tissue  $\text{Ca}^{2+}$ . Some toxins causing cardiac arrest in systole make the SR leaky to  $\text{Ca}^{2+}$ .

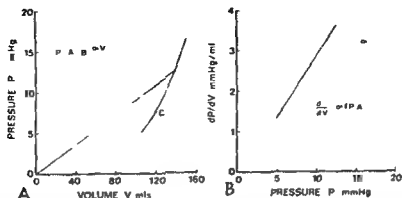


Fig 3 Pressure-volume relations. A The P-V relationship at end-diastole (ed) is exponential (slope a) B Relationship between pressure P and  $dP/dV$  (chamber stiffness) The curve is linear with slope a (modulus of chamber stiffness) (Reproduced from Murky 1 by permission of *Progress in Cardiovascular Diseases*)

The system is also pH dependent. Moreover there is evidence that a primary inotropic effect of adrenaline apart from its effects on membrane conductance (where it increases conductance during the plateau phase to elevate the plateau potential and increase action potential duration effects which increase tension in frog ventricle) may be to stimulate sequestration of  $Ca^{2+}$  in the cell via a cyclic amp mechanism—i.e. to increase relaxation of tension to facilitate recirculation of the  $Ca^{2+}$  pool. The effect is mediated by beta adrenergic receptors and can be blocked by substances which block the beta receptors.

2 Extracellular extrusion of  $Ca^{2+}$  is related to the sarcolemmal  $Na^{+}/Ca^{2+}$  exchange mechanism. In frog heart experiments the rate of relaxation decreases with an increase in intracellular  $Na^{+}$  and a fall in the  $Na^{+}$  gradient.<sup>1</sup>

■ In addition to the rapid mechanisms permitting relaxation after each contraction there are cellular  $Ca^{2+}$  buffers located in the mitochondria, the SR and possibly in the troponin and other regulatory or contractile proteins as well as in glycoproteins and glycolipids of the basement membrane.

Mechanical factors which may be important in relaxation are the decreased force generated by the same calcium at shorter muscle lengths (deactivation) and the relations between peak tension and the rate of relaxation. If sarcomere length is held constant during early relaxation developed tension falls more rapidly than when over all muscle length is kept constant. Moreover there is non uniformity in sarcomere length and sarcomere length dispersion increases in the interval between contractions without a change in resting tension.<sup>1</sup>

### Aspects of relaxation and compliance in the intact heart

The problem of cardiac relaxation in the intact heart revolves essentially around the diastolic stiffness properties of the left ventricle (LV). The stiffness or compliance of the LV may be considered at two levels: (1) at the level of the intact pumping chamber—the situation in the intact animal and in the intact patient (LV chamber stiffness or compliance) and (2) at the level of a unit of myocardium (muscle stiffness and muscle compliance).

**Chamber compliance of the left ventricle.** Left ventricular filling takes place in diastole and as the LV fills its pressure rises. Studies of ventricular compliance were originally based on measurements of LV end diastolic pressure (LVEDP)<sup>1</sup> and later on the relationship of the LVEDP to end diastolic volume (V) on the total pressure change during diastole ( $\Delta P$ ) or on change in pressure ( $\Delta P$ ) for given change in ventricular volume ( $\Delta V$ ). LV stiffness is given by the change in pressure for a given change in volume ( $\Delta P/\Delta V$ ) and LV compliance or distensibility by its reciprocal  $\Delta V/\Delta P$  while specific compliance is calculated by correcting for LV cavity size ( $\Delta V/V\Delta P$ ). These measurements can be made as the mean change over the whole of diastole (i.e. as a chord to the diastolic P-V curve) or by considering limiting boundaries ( $\Delta V \rightarrow 0$ ) and by measuring the slope as a tangent to the curve at any point during diastole.  $dP/dV$  therefore gives instantaneous operative volume stiffness and  $dV/dP$  gives instantaneous chamber distensibility or chamber compliance. Since the LV pressure-volume curve is in general terms exponential (Fig 2)  $dV/dP$  decreases as ventricular volume increases.

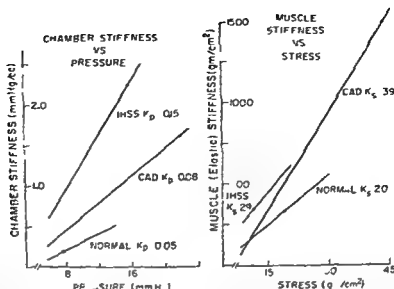


Fig 4 Relations between "chamber stiffness" and pressure (left hand panel) and "muscle stiffness" and stress (right hand panel) in a normal subject patient with coronary artery disease (CAD) and hypertrophic cardiomyopathy (IHSS). The modulus of chamber stiffness  $k_p$  is increased in CAD and increased further in IHSS. When muscle stiffness is considered however the modulus  $k_s$  is highest in CAD and only mildly increased in IHSS. Operative muscle stiffness is normal in IHSS since actual stress is low. Both operative stress and muscle stiffness are very high in CAD. (Reproduced from Gaasch and colleagues by permission of the American Journal of Cardiology.)

so that simple volume loading of an otherwise normal ventricle causes a decrease in LV compliance (or increase in stiffness) and an increased end-diastolic pressure.<sup>1</sup> The rate of change of chamber stiffness with increasing P (the modulus of chamber stiffness) is given by  $k_p$  or  $\alpha$  (Figs 2 and 3). Algebraically this may be written

$$P = be^{k_p V}$$

$$\ln P = \ln b + \ln b$$

$$k_p = (\ln P - \ln b)/V$$

An increase in  $k_p$  occurs in cardiac disease associated with LV hypertrophy and/or fibrosis. An increase in  $k_p$  means that the ventricle is more stiff at any given ventricular volume and the diastolic ventricular pressures increase. A decrease in LV compliance (increase in stiffness) may be the consequence then of (1) an increase in ventricular volume or (2) of a change in the modulus of chamber stiffness ( $k_p$ ) or (3) a combination of the two mechanisms (Fig 2) (Table I). On the other hand a decrease in the modulus of chamber stiffness occurs in chronic LV volume overload—e.g., chronic aortic incompetence mitral incompetence congenital VSD.  $k_p$  decreases and large volume loads are handled at a relatively low end-diastolic pressure. The mechanism of the change is not clear; it may be related to myocardial fiber slippage, reduplication of sarcomeres (in

series and in parallel) or to pericardial changes.<sup>22</sup>

**Muscle stiffness and muscle compliance.** The stiffness properties of the myocardium are described by the stress-strain relations of a unit of myocardium.<sup>23</sup> The mathematics and calculation of muscle stiffness are analogous to that of chamber (volume) stiffness but stress is used instead of pressure and strain for volume. The instantaneous stiffness of a unit of myocardium is given by the tangent to the stress-strain curve ( $E$  or tangent modulus). The modulus of muscle stiffness ( $k_s$ ) is the rate of change of  $E$  for an increase in stress (Fig 4).

The distinction between LV chamber stiffness and muscle stiffness is important since operative chamber stiffness depends not only on the stiffness of the muscle but also on ventricular loading conditions and ventricular muscle mass. An increase in muscle mass increases operative chamber stiffness; filling is impaired in the hypertrophied ventricle and diastolic pressures may be high despite normal or relatively normal stiffness properties of each unit of myocardium. The difference between chamber and muscle stiffness is shown in Fig 4 for patients with hypertrophic cardiomyopathy (HOCM), coronary artery disease (CAD) and in a normal subject.<sup>24</sup> In HOCM, chamber stiffness is high and the curve is very

steep ( $k_p$  very high) while in CAD chamber stiffness and its modulus  $k_p$  are increased less. When muscle stiffness  $E$  and its modulus  $k$  are considered however it is clear that in HOCM  $k_p$  is only slightly increased while in CAD  $k_p$  is twice normal and muscle stiffness is very high. It follows then that in HOCM  $k_p$  is high and the diastolic P-V curve is steep because of ventricular hypertrophy and a change in cavity geometry. In CAD the steep P-V curve is the consequence of an increase in intrinsic muscle stiffness, the result of ventricular fibrosis.

#### The LV volume-mass ratio

The normal LV volume/mass ratio (V/M ratio) is just less than 1.0 (LVEDV 70 ml/M, LV wall mass 90 g/M<sup>2</sup>). It has been shown that myocardial stiffness and its modulus  $k$  may be estimated from the product of  $k_p$  and the V/M ratio. In HOCM  $k_p$  is high, there is great muscle hypertrophy with a low V/M ratio and muscle stiffness ( $k$ ) may be normal. In contrast in patients with coronary artery disease  $k_p$  is again high but the normal or near normal V/M ratio suggests that muscle stiffness and  $k$  are high because of ventricular fibrosis in the region of myocardial damage.

Chronic volume loading is associated with a normal V/M ratio.  $k_p$  is reduced presumably the result of a decreased  $k$ . Acute volume loading is accompanied by a high LVEDP, little change in  $k_p$ , an increase in V/M and a high  $k$ . These data have been well summarized by Gaasch and colleagues.

#### LV compliance throughout diastole

Until recently most studies described LV pressure-volume and stress-strain relations at selected points at end diastole at early and end diastole or at different points during diastole. It had been assumed that the LV diastolic P-V relationship was exponential but while data taken from a single point at end diastole may produce exponential curves in animal studies and in inter or intra patient studies these data apply to end diastole only. It is not necessarily true that the LV P-V curve is exponential throughout diastole. On the contrary the tangent modulus  $E$  changes markedly during the different phases of diastole with an extremely low value when calculated in mid diastole during the slow filling phase. Present studies are directed at characterizing the stiffness properties of the myocar-

**Table 1** Some diseases associated with decreased LV compliance

- 1 Increased LV volume ( $k$  unchanged)
  - a Fluid overload due to anaemia renal failure over transfusion
  - b Valvular incompetence (mitral and especially aortic)
  - c Left to-right shunts or arteriovenous fistulas
- 2 Increased modulus of chamber stiffness ( $k_p$ )
  - a Increased stiffness of the LV chamber due to geometrical changes of ventricular hypertrophy (AS HOCM hypertension)
  - b Abnormal intrinsic muscle stiffness ( $k$ )
    - damaged LV muscle with scar tissue (coronary artery disease LV fibrosis)
    - cardiac infiltrative disorders (amyloidosis)
    - pericardial changes (constrictive pericarditis)

In chronic volume overload changes in the modulus of chamber stiffness  $k_p$  may offset the expected increase in LV stiffness due to the increase in ventricular volumes.

dium during the different phases of ventricular diastole.

#### Other measurements of ventricular relaxation

1 **Negative LV dp/dt** The peak rate of fall of LV pressure (peak neg dp/dt) usually occurs during the isovolumic relaxation period and has been used as a measurement of early diastolic relaxation but depends on end systolic volume and pressure.<sup>1</sup> The time course of relaxation ( $T$ ) derived from the rate constant of the exponential pressure decline during isovolumic diastole subsequent to the occurrence of peak neg dp/dt may be a better index of early diastolic relaxation. It seems to be independent of peak systolic pressure, end systolic volume and fiber length.<sup>23</sup> Both peak neg dp/dt and  $T$  are abnormal in patients with coronary artery disease during pacing induced angina<sup>2, 4</sup> and suggest that impaired early ventricular relaxation may be responsible for the rise in end diastolic pressure which occurs later in diastole. Peak neg dp/dt is related to peak pos dp/dt and is also abnormal in congestive cardiomyopathy where it has been suggested that both impaired ventricular contraction and relaxation are important in the pathogenesis of the disease.<sup>24</sup>

2 **Rate and pattern of LV filling and the isovolumic relaxation period** The normal LV relaxes rapidly in early diastole so that a large volume of blood enters immediately after mitral valve opening. By the time the 0 point is reached up to 50 per cent of ventricular filling may have



occurred another 30 to 40 per cent occurs by the end of the rapid filling phase, there is little change during slow filling and atrial systole delivers the last 5 to 10 per cent of the volume filling the LV. The instantaneous LV filling rate can be measured from digitization of the angiocardio gram or echocardiogram to show abnormalities both in the timing and rate of ventricular filling. The subject has been studied by Gibson and colleagues<sup>1</sup> who have shown abnormal LV filling rates and times and abnormal wall thinning in patients with abnormal LV chamber compliance (hypertrophic cardiomyopathy). These authors have also drawn attention to the presence of abnormal ventricular wall movement during the isovolumic relaxation period in patients with coronary artery disease<sup>2,3</sup> "patients with CAD and regional asynergy have important changes in LV diameter with abnormal inward or outward movement of the ventricular wall during the isovolumic relaxation period depending on whether the abnormal or normal segment is studied. Displacement-diameter loops are constructed from the echo and apexcardiogram by digitizing the tracings and computer processing."

#### Effect of the pericardium and right ventricle

Studies of the diastolic properties of the LV in the intact heart must take into account the effect of changes in right heart function and the pericardium. Right ventricular abnormalities and right ventricular hypertrophy are accompanied by changes in septal and free LV wall thickness and abnormal left ventricular pressure-volume relations.<sup>4</sup> Similarly, pericardial disease (effusion or constriction) causes abnormal function of the LV in diastole. The importance of the pericardium and the right ventricle is not certain in primary diseases of the left ventricle but may be greater than thought previously. Indeed in patients with left ventricular volume overload the difference between the steep pressure-volume curve and very high LV end diastolic pressure of the acute situation (e.g. acute AI) and the flatter P-V curve of chronic disease may be that of pericardial adaptation to the increased volume over a period of time. Similarly a large pericardial effusion (1000 to 2000 ml) may be tolerated reasonably well if it accumulates over a period of weeks to months but acute cardiac tamponade occurs if a smaller volume of fluid accumulates

rapidly. In patients with congestive cardiomyopathy, some improvement in the clinical state has been reported after pericardiectomy.<sup>5</sup>

#### Clinical methods in studies of ventricular compliance

Calculation of the indices of chamber and muscle stiffness requires simultaneous measurement of ventricular geometry (cavity size shape and wall thickness) and intraventricular pressure. This means that at present an invasive procedure is required. Intracardiac pressure should be measured using a catheter tip micromanometer. The frequency response of a good fluid filled catheter manometer system may be flat to 15 to 20 Hz but LV pressure falls rapidly in early diastole to 2 to 5 mm Hg at the 0 point. Any error due to overshoot or resonance is important and significant at this level of pressure. Measurements of end diastolic pressure are more accurate but we believe that all modern detailed studies of diastole should be made with the greatest possible accuracy using an intracardiac micromanometer.

Accurate measurement of LV geometry and LV volume change is also difficult. Angiocardiology provides details of LV cavity shape and size. Measurements of free wall thickness can be obtained. Both uniplane and biplane methods have been used but it must be remembered that studies based on single plane angiography are less accurate especially at beginning diastole and in patients with coronary artery disease and regional ventricular asynergy. Moreover angiography opacifies the LV for only 5 to 10 beats and respiratory maneuvers during filming and the rapid injection of contrast medium may alter ventricular dynamics. The procedure cannot be repeated more than once or twice. Echocardiography on the other hand provides accurate measurement of ventricular cavity dimensions and wall thickness (including both septum and posterior free wall) does not upset the patient's hemodynamic state and can be repeated at will. The M mode echo however, provides limited views of the left ventricle and does not provide data relating to overall cavity shape information which is necessary for the calculation of wall stress. Cross sectional echocardiography may be useful in studies of LV pressure-volume and stress-strain relations but the quality of the image must be adequate to identify accurately.

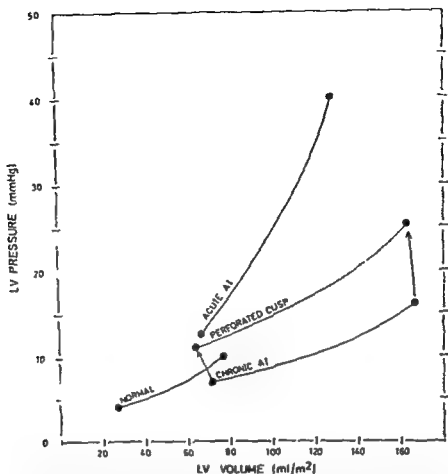


Fig 5 Diastolic pressure-volume curves of the left ventricle (LV) in aortic incompetence (AI) plotted as a chord from the 0 point to LV end-diastolic pressure. In acute AI the patient is shifted up a normal P-V curve and end-diastolic pressure and  $dP/dV$  are very high. In chronic AI the modulus of chamber stiffness has decreased the curve is less steep and a large volume load is handled at a relatively low end diastolic pressure and  $dP/dV$ . (Reproduced from Lewis H S and associates with permission of *Israel Journal of Medical Sciences*)

and specifically both endo- and epicardium.

Lastly, the importance of recording ventricular pressure and volume simultaneously should be noted. Earlier studies which relate end-systolic volume to the 0 point in the LV pressure pulse tracing underestimate LV volume at this time since appreciable left ventricular filling occurs immediately after mitral valve opening.

#### Abnormal geometry

Calculation of wall stress requires detailed information relating to LV cavity geometry. The left ventricle has been likened to an ellipsoid and several formulas have been derived for wall stress; most authors using a thick-walled model in which shear stresses and bending moments are neglected. It seems preferable to base a model on large deformation theory. The use of simpler

formulas using spherical geometry may provide similar results. In any event the shape of the ventricle changes during systole and diastole and especially so in patients with cardiac dilatation or regional ventricular dysfunction. Moreover, fiber orientation is extremely variable at different sites in the ventricular wall and there is at present no way to take this into account in the intact patient. The distribution of muscle fiber stress from epicardium to endocardium is not necessarily linear and predictable. Computer analysis has greatly facilitated studies of these problems in analyses of ventricular diastole. The computer has been invaluable in modelling, in making calculations from digitized data and in the development of mathematical models using finite element theory which may be useful in a more detailed analysis of regional muscle function.<sup>10, 15, 22</sup>

## Left ventricular compliance in clinical cardiac disease

### Left ventricular volume overload

**1 Acute volume overload** Chamber compliance is greatly decreased as the ventricle unprepared for the sudden large volume load is shifted upwards along its pressure-volume curve (Fig 5). In acute aortic incompetence the end diastolic pressure increases markedly to 50 to 60 mm Hg<sup>34</sup> and the patient develops severe left heart failure with pulmonary edema. In acute mitral incompetence there is again a significant decrease in LV compliance as ventricular volume increases; the end diastolic pressure is usually lower than in acute aortic incompetence since systolic ventricular emptying is facilitated in acute mitral incompetence by the sudden decrease in ventricular afterload. There is less information regarding *muscle stiffness* in acute aortic or mitral incompetence. The cavity dilates; the wall is thin and muscle fiber stress is high. The tangent modulus  $E$  is high since operative stress is increased. The volume-mass ratio increases;  $k$  is probably normal.

**2 Chronic volume overload** In chronic rheumatic mitral and aortic incompetence the ventricle adapts with a decrease in the modulus of chamber stiffness ( $k_c$ ) so that large volumes are handled at relatively low end diastolic pressures<sup>35</sup> (Fig 5). Chronic aortic or mitral incompetence may be well tolerated clinically for many years.

The precise mechanism for the change in chamber stiffness is uncertain; it may be due to changes in myocardial fiber arrangement or to pericardial adaptation. It has been suggested that *muscle stiffness* should increase with ventricular fibrosis and hypertrophy.

**Left ventricular pressure load and ventricular hypertrophy** Studies have been made in aortic stenosis and in hypertrophic cardiomyopathy (HOCM IHSS). LV hypertrophy is accompanied by an important increase in the modulus of LV chamber stiffness ( $k_c$ ). The slope of the P-V curve is steep and operative end diastolic pressure and compliance are high.

Measurements of *muscle stiffness* provide interesting results. While some patients with aortic stenosis have an important increase in muscle stiffness,  $k$  is only moderately abnormal in other patients despite a large increase in LV chamber stiffness.<sup>36-38</sup> This may be predicted from the decrease in the LV volume/mass ratio which occurs in aortic stenosis and in HOCM. Operative

stress may be low in patients with HOCM. The distinction between measurements of chamber compliance and muscle compliance is therefore crucial in modern studies of ventricular relaxation and diastole (Fig 4).

**Coronary artery disease** Ventricular damage is segmental in CAD; measured changes in overall chamber stiffness are the result of changes in *muscle stiffness* in the abnormal ischemic zone(s) in the boundary layer and in the remaining healthy myocardium. Myocardial ischemia interferes with myocardial relaxation; muscle stiffness and its modulus  $k$  increase and total ventricular chamber compliance falls. There may be a shift to a steeper P-V curve (increased  $k_c$ ) or the whole LV P-V curve moves upwards, resulting in a high end diastolic pressure. In pacing-induced angina there is a fall in  $-\text{neg } dp/dt^{39,40}$ —i.e., an abnormality of early diastolic relaxation—and this contributes to the higher diastolic pressures later in diastole. Similar events occur after myocardial infarction, but in angina pectoris the changes are reversible. In myocardial infarction an early increase in compliance has been observed in some experimental animal studies using sudden coronary occlusion. This may be due to stress relaxation<sup>41</sup> or simply to the abrupt cut off of coronary blood flow with a fall in myocardial turgidity.<sup>42,43</sup> In the days following myocardial infarction there is stiffening of the infarcted area to improve the mechanical disadvantage of the dyskinetic area during systole; stiffness is high 5 to 8 days after the infarct and the high muscle stiffness is maintained as permanent fibrosis of the infarcted area occurs. LV chamber stiffness and LV P-V relations usually remain abnormal after myocardial infarction if the infarcted area is sufficiently large.<sup>44</sup> Fibrous aneurysms resected from human left ventricle have higher stiffness values than do muscular aneurysms.

**Myocardial disease** In primary myocardial disease the LV is greatly dilated with poor systolic function.<sup>45</sup> Ventricular volumes are large; the stroke volume is small and operative end diastolic pressure is high. In myocarditis with acute LV dilatation LV chamber stiffness and presumably wall stress are high. There is severe LV failure. In chronic myocardial failure (congestive cardiomyopathy) chamber stiffness and its modulus (measured as a chord from early to end diastole) are slightly decreased perhaps again an adaptation to chronic volume loading.<sup>46</sup>

The range of values is large an expected finding in this disease of uncertain etiology where we may be examining a heterogeneous population. We found that operative end diastolic fiber stress is increased while Mirsky and associates<sup>4</sup> showed an increase in both elastic stiffness and  $k$ . Peak negative  $dp/dt$  is decreased.

Infiltrative cardiomyopathy (e.g. amyloidosis) is associated with a normal sized LV with relatively normal systolic function but stiff muscle presumably (high  $k$ ) the LVEDP is increased.<sup>1</sup>

**Constrictive pericarditis.** In constrictive pericarditis pericardial fibrosis and/or calcification limits ventricular filling.<sup>1</sup> Peak negative  $dp/dt$  is moderately reduced<sup>10</sup> the 0 point of the LV pressure pulse tracing is increased and rapid ventricular filling ends with a palpable and audible early diastolic filling halt (third heart sound). During slow ventricular filling there is little further change in LV pressure and volume and the a wave is relatively unimportant in most patients. To make meaningful analysis of ventricular relaxation and filling in constrictive pericarditis diastole should be analyzed continuously since the relative contribution of myocardial and pericardial factors to overall chamber stiffness almost certainly changes in the different phases of diastole. However most studies until now have measured over all diastolic function of the LV.<sup>11</sup> The overall P-V curve (measured as a chord from the 0 point to end diastole) is shifted upwards and to the left. Ventricular volumes are small while chamber stiffness and its modulus  $k_p$  are increased. There have been no studies which measure LV wall stress and stress-strain relations. Such studies should ideally examine the relative contributions of myocardium and thickened pericardium to total ventricular wall thickness and compliance.

**Effect of premature ventricular contractions.** There is no change in the modulus of chamber stiffness after the ectopic beat or after the post extrasystolic beat in normal man and in conscious dogs. Increased filling during the post extrasystolic pause causes the ventricle to operate higher on the steep (stiffer) portion of its pressure-volume curve. There is a preload dependent change in compliance without a change in stiffness modulus. The diastolic properties of a failing ventricle with an increased EDP may differ though and earlier studies showed variable diastolic compliance after extrasystoles.<sup>12</sup> In these ventricles

increased compliance was seen in the immediate post extrasystolic pause.

**Effect of drugs changes in preload and afterload.** Nitroglycerin improves LV chamber compliance by reducing preload and afterload. Ventricular volume decreases and end diastolic stress and pressure fall as the ventricle moves down its compliance curve (Fig 2). In addition (as with sodium nitroprusside) there is a downward shift in the entire pressure-volume curve without a change in its slope  $k_p$ . The time course  $T$  of relaxation is not altered and it has been suggested that the change in the curve may be the result of a change in external constraints of LV filling such as decreased RV filling.<sup>13</sup> The decrease in LV end diastolic pressure permits improved diastolic coronary filling, there is improved myocardial oxygenation and this leads to further improvement in LV compliance as ischemia is relieved and muscle stiffness falls.

**Sodium nitroprusside** decreases ventricular afterload and ventricular volume decreases (as a result of better systolic emptying). Sodium nitroprusside also affects the diastolic properties of the LV and there is a downward shift of the LV P-V curve so that for any given volume pressure is lower.

**Effect of beta adrenergic blocking drugs.** Propranolol has been found to increase end diastolic volume for a given end diastolic pressure (increased LV compliance) in patients with coronary artery disease and impaired systolic function.<sup>14</sup> There was no difference however in the slope  $k_p$  of the log P volume curve in patients with CAD. We do not have data relating to the effect of beta blockade on muscle stiffness in CAD.

In hypertrophic cardiomyopathy (HOCM) acebutolol has been shown to decrease both beginning and end diastolic ventricular pressure at similar LV volumes again implying increased LV compliance but there was again no change in the modulus of chamber stiffness  $k_p$ . Calculation of  $k_p$  was less accurate in this study, however since pressure and volume were not recorded simultaneously and there are no data relating to muscle stiffness and  $k$ .

#### Unanswered questions

Studies of diastole have provided a large amount of information about ventricular relaxation and filling but there are many unanswered questions. Which is the primary step in the

cardiac relaxation process? What is the precise correlation between molecular and biochemical processes and events in the intact heart? What is the importance of plasticity and viscosity and the relation between static and dynamic compliance? The time course of relaxation requires extensive study, as does a detailed analysis of instantaneous LV muscle and chamber function during each phase of diastole in different diseases. There is little detailed information relating to changes in ventricular muscle and chamber distensibility after medical or surgical intervention and little information relating to the prognostic significance of such changes.<sup>1-3</sup>

The relation between the hemodynamic data and the clinical picture is interesting but not completely understood. Increased diastolic pressures cause left atrial and pulmonary venous hypertension with shortness of breath and in many patients an additional third and/or fourth heart sound. The precise setting for the genesis of a third or fourth heart sound in a given patient with decreased LV compliance is uncertain. A third heart sound is usually found in a large dilated left ventricle. It appears that ventricular filling is sufficient to produce the change of momentum required for a third heart sound at the end of the rapid filling phase in these patients since according to the Laplace relationship a large ventricle can distend fairly rapidly in the first third of diastole while the relative contribution of atrial systole later in diastole need be small or moderate. On the other hand a fourth heart sound is usually heard in a non-compliant ventricle of normal or decreased cavity size where atrial filling contributes a relatively large volume of blood to total ventricular filling. It is possible that a thick walled ventricle with small cavity size expands with difficulty in the first part of diastole and there is thus insufficient volume transfer and change of momentum during this period to produce the energy required for a third heart sound. The quantitative importance of the LV volume/mass ratio and the moduli of chamber and muscle stiffness in this regard are not certain. Studies of LV filling patterns in relation to other measurements of ventricular relaxation may supply more precise data as to the precise pathophysiological mechanisms underlying the genesis of third and fourth heart sounds in individual patients.

Finally, the use of the term "cardiac failure

and congestive heart failure should now be reviewed. Traditionally these terms were used to describe patients with the physical signs of an elevated jugular venous pressure, hepatomegaly, edema, shortness of breath and chest rales. These are all signs of elevated diastolic filling pressure (right or left sided) and really indicate abnormal LV chamber compliance, the result of several possible mechanisms (Table I)—increased ventricular volume or an increased modulus of chamber stiffness due to hypertrophy and geometrical changes with or without additional changes in intrinsic muscle stiffness and  $k$ . In some patients with cardiac failure, systolic ventricular function and cardiac output are normal or increased; in others cardiac output is low. The patients are cold, sweaty, have a low blood pressure and may be in a state of shock. The terms "low output failure" and "high output failure" were used to distinguish patients with a low cardiac output from those who maintained good or adequate systolic LV performance despite the signs of congestive heart failure. High output failure occurs in conditions such as beriberi and anemia, where systolic muscle function is increased, normal or relatively normal despite the diastolic compliance abnormality. It seems then that at this time the clinical cardiologist should better describe the actual physical findings in a given patient and interpret these in terms of (1) abnormalities of systolic pump performance and (2) abnormalities of diastolic ventricular compliance. General terms such as "cardiac failure" or "congestive heart failure" are no longer adequate for the cardiologist to describe with accuracy the pathophysiological hemodynamic abnormalities in heart disease or to guide in their treatment.

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# Fundamentals of clinical cardiology

## Nitrate tolerance and dependence

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Nitroglycerin (NTG: glyceryl trinitrate) and other organic nitrates are widely used in the care of patients with cardiovascular disease. Long acting nitrates, once viewed as ineffective by many investigators<sup>1</sup>, are now accepted as physiologically active compounds that maintain their effect over many hours<sup>2</sup>.

The problem of tolerance to organic nitrates has been raised since the first clinical reports of NTG therapy for hypertension in Bright's disease. In 1888 Stewart reported a case of NTG tolerance in a man who required 20 grains of pure NTG to achieve the same hypotensive effect as the initial dose of 1/100 grain<sup>3</sup>. He later stressed that this was a common problem in clinical practice<sup>4</sup>. Many other workers, including well known pharmacologists<sup>5,6</sup>, have subsequently cautioned physicians about the potential problem of NTG tolerance. Prominent clinicians have continued to raise questions about nitrate tolerance and have left the issue unresolved<sup>7</sup>. Others have strongly stated that tolerance is not an important clinical problem<sup>8</sup>. A major source of concern has come from the explosives industry, where a multitude of reports from 1898 to the 1960's have unequivocally documented withdrawal symptoms in workers daily exposed to nitrate compounds who are temporarily away from the work environment<sup>9</sup>. Although the munitions industry experience has been noted in the clinical literature, Morton recently stated that nonoccupational physicians have taken too little heed of the industrial evidence regarding NTG tolerance and has recommended further study.

### Nitrate tolerance revisited

Until the mid 1970's the question of nitrate tolerance in cardiovascular disease had been relatively unimportant. The utilization of large amounts of sublingual NTG in patients with angina has rarely been noted to result in significant tolerance even in individuals using huge quantities (20 tablets or more) daily. Long acting nitrates were considered to be ineffective by most clinicians and many prominent investigators were adamant in their view that these agents had no role in clinical medicine<sup>1-4</sup>.

The advent of propranolol therapy for angina, rapidly followed by the widespread application of coronary bypass grafting, seemed to further vitiate the potential usefulness of these agents. Two related phenomena have dramatically changed the perspective on these drugs: (1) There have been a considerable number of recent well conducted clinical investigations that convincingly document the efficacy of long acting nitrates in the treatment of angina pectoris<sup>10-12</sup>. Studies have proved beyond reasonable doubt that these agents can provide prolonged chest pain relief for patients with angina. Exercise tolerance, ischemic ST response to exercise, and frequency of sublingual NTG consumption are all improved with judicious utilization of long acting nitrates. (2) The advent of vasodilator therapy for congestive heart failure has provided a valuable new arena for long acting nitrates and a large number of studies have proved that these agents have a potent and prolonged physiologic effects<sup>13-15</sup>. Vasodilator therapy presently plays an integral role in the therapy of moderately severe congestive heart failure. Nitrate formulations that are currently in widespread use are listed in Table I.

For these reasons the question of nitrate tolerance and dependence takes on a new urgency in 1980. Nitrates are being used in large numbers of patients with cardiac disease and have become

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Table 1 Clinically available nitrate drugs

## Nitroglycerin (glyceryl trinitrate) formulations

- Sublingual
- Oral
- Oral sustained action
- Ointment

## Synthetic organic nitrates

- Isosorbide dinitrate
  - Oral
  - Oral sustained action
  - Sublingual
  - Chewable

## Isosorbide tetranitrate

- Oral
- Oral sustained action

## Erythritol tetranitrate

- Oral
- Sublingual
- Chewable

## routine adjunctive therapy in heart failure.

There is increasing experience with high-dose organic nitrate formulation. Isosorbide dinitrate (ISD) regimens of 20 to 40 mg, three to four times a day or more have been given in a number of recent studies. Previous animal and human data suggest that nitrate tolerance is more readily induced with large doses of nitrates. It is thus timely to reexamine the evidence for nitrate tolerance and dependence and to carefully evaluate recent clinical studies that deal with this problem.

## Definitions

**Tolerance** to a drug exists when increasing dosage is required to obtain a given therapeutic effect.<sup>1</sup> It is a general phenomenon seen with a wide variety of agents, particularly those affecting the central nervous system. The mechanisms underlying tolerance are poorly understood and may involve multiple complex and independent phenomena. It is common to acquire tolerance to some but not all of a drug's actions and to have varying degrees of tolerance with respect to different drug effects. Often drug activity is of short-ened duration and lesser intensity in the tolerant subject. The requisite lethal dose may increase enormously. Tolerance classically disappears after cessation of drug therapy and develops again after an appropriate period following reinstitution of the drug.

**Cross tolerance** often occurs with related compounds and implies that more than one agent

can induce tolerance to a given drug. A single drug may produce tolerance to other similar drugs.

**Dependence** on a drug means that psychological and/or physical symptoms will appear when the substance is discontinued.<sup>2</sup> **Withdrawal symptoms** are typical of various mood and behavior-altering drugs including alcohol, opiate, amphetamines, and sedative hypnotics. Frequently there is a rebound effect with apparent increased "susceptibility" of physiologic systems affected by the compound. There can be cross-dependence among related drugs. Although tolerance and physical dependence commonly occur together, one may exist without the other.<sup>3</sup> This is important to keep in mind when considering nitrate effects: both tolerance and dependence may be implicated in some subjects but either phenomenon can be an isolated problem or others.

## Evidence supporting nitrate tolerance and dependence

**Clinical experience.** NTG was initially used for the treatment of hypertension.<sup>4</sup> Mild to severe headaches are commonly encountered; these often disappear with continued drug treatment. Countless reports have documented this sequence, including many contemporary studies. This strongly suggests the development of acquired tolerance to the cerebral vasodilator actions of NTG. Other nitrate side effects such as dizziness and nausea may also abate after several days of therapy. This phenomenon is also true for organic nitrates such as ISD: headaches are common early in therapy but tend to disappear with continued therapy.

There are anecdotal reports of patients who lose their clinical response to NTG and require increased NTG dosage. These cases are quite uncommon and find scant documentation in the literature.

**Munitions industry experience.** The most impressive evidence for nitrate tolerance and dependence comes from the industrial experience in explosives manufacturing plants. NTG and ethylene glycol dinitrate (nitroglycol) are fundamental components of dynamite and other explosives. These agents are strongly implicated in a whole array of medical problems seen in factor workers exposed to these agents. A characteristic syndrome has been recognized since 1898.<sup>5</sup> The

consists of the occurrence of mild to severe headaches (powder headaches) in exposed workers at the end of weekend breaks or other layoffs from work. Characteristically the headaches begin Sunday or early Monday morning approximately 48 to 72 hours after the employee is absent from the nitrate laden environment. Workers are known to rub NTG into their skin or use impregnated headbands on weekends to avoid these headaches. Some take medicinal NTG for this purpose. Studies of munitions factory employees have demonstrated decreased systolic blood pressure, decreased pulse pressure, increased heart rate and abnormal finger pulse wave contours. These abnormalities completely disappear when the worker is removed from nitrate exposure for 24 to 72 hours. Similar experiences have been documented in pharmaceutical NTG workers. Isolated reports of these problems appeared in the European literature<sup>2,3</sup> and less often in the United States in industrial medicine publications<sup>4,5</sup>.

Widespread medical awareness of the risks of industrial nitrate exposure in this country followed the report of Lange and associates in 1972 when vastly more serious sequelae of dynamite manufacturing were reported i.e. chest pain and sudden death. Europeans had described this phenomenon years earlier. In 1952 a German report first documented three cases of sudden death among nitroglycol workers.<sup>6</sup> These authors surveyed the world industrial experience and turned up 44 other deaths, 37 from the United States. Other similar reports appeared in the European literature. The first United States report came in 1963 following a careful investigation into a number of deaths occurring in several Pennsylvania dynamite plants. This excellent paper was ignored by clinicians and in fact a review of the toxicity of NTG in 1965 failed to cite either the European or United States experience of nitrate related chest pain syndromes and sudden death.

Characteristically exposed workers complain of nonexertional substernal chest pressure or pain on the Sunday or Monday following a weekend break from work. The pains may be mild or severe. A number of deaths as well as acute myocardial infarctions have been documented.

It has been postulated that withdrawal from nitroglycerin or nitroglycol results in unopposed (reflex) coronary and systemic vaso-

constriction with subsequent coronary ischemia, elevated diastolic blood pressures and lowered systolic and pulse pressures in exposed workers lend credence to the theory of rebound vasoconstriction. Of great importance was the documentation by coronary arteriography of normal coronary arteries in four such individuals and coronary vasospasm in one with recurrent chest pain. More recently Klock<sup>7</sup> also documented coronary vasospasm with normal vessels in a young male dynamite worker with severe chest pain occurring when he was unexposed to the work environment. Workers who have chest pain syndromes generally become permanently free of symptoms upon long term removal from nitrate exposure.

These cases all support the concept that withdrawal coronary vasospasm does occur in some munitions workers who are chronically exposed to nitrates. This dependence poses an enormous health hazard. Industrial hygiene and public safety groups have recommended strict criteria for protection of munitions workers.<sup>8</sup> It has been well established that both NTG and nitroglycol penetrate clothing and protective gloves and rigorous techniques are necessary to prevent cutaneous absorption of the offending substances. Nitroglycol is also present in vapor form in the ambient air and can be absorbed through the respiratory system. Both substances are present in explosives manufacturing and it is unclear whether one or both are responsible for the various withdrawal syndromes. Klock,<sup>7</sup> Carmichael and Lieben<sup>9</sup> and others<sup>10</sup> have even suggested that chronic NTG exposure may lead to accelerated atherosclerosis in these workers. Hueper and Landsberg<sup>11</sup> produced degenerative vascular lesions in young rats by chronic nitrite and nitrate exposure and believe this may explain the atherosclerosis seen in chronic nitrite poisoning. They postulated that protracted vasodilatation interferes with normal coronary artery nutrient blood supply and results in vascular injury. This theory seems unlikely and requires more research before any firm conclusions can be drawn. The evidence that munitions workers do in fact have increased atherosclerosis is only anecdotal.<sup>12</sup>

It is thus indisputably clear that chronic exposure to high concentrations of NTG or organic nitrates can result in tolerance (disappearance of headaches after several days of work) and de-

pendence (Monday syndrome chest pain myocardial infarction) Whether this unusual industrial hazard has any relevance to patients given far smaller and much more intermittent exposure to nitrates is certainly debatable.

**Animal studies** Tolerance to NTG has been readily produced in rats<sup>22, 23</sup> rabbits<sup>24</sup> and dogs<sup>25</sup> and the degree of tolerance is directly related to the size of the dose administered. Decreased responsiveness to nitrates rapidly develops and when massive amounts of NTG are used vascular smooth muscle may become totally insensitive to repeat nitrate administration. Even a single dose of NTG in rats can produce some tolerance. Tolerance rapidly disappears after cessation of nitrate administration. Experiments by Needleman and Johnson<sup>26</sup> and Needleman<sup>27</sup> have excluded decreased availability of free drug, tissue exhaustion, increased biotransformation or increased sympathetic activity as mechanisms for tolerance. In a subsequent discussion Needleman and Johnson<sup>28</sup> proposed that the cellular mechanism of tolerance to NTG is a result of nitrate induced oxidation of sulfhydryl groups in vascular smooth muscle nitrate receptor sites. Organic nitrates act at these receptors to produce vascular relaxation. The disulfide receptor has less affinity for NTG. In animals made tolerant to NTG they were able to reverse the *in vitro* loss of nitrate sensitivity by exposing the vascular wall to a disulfide reducing agent thus returning vessel reactivity to normal. Cross tolerance was easily produced to NTG by a group of organic nitrates.<sup>29</sup> Cohen and Kirk<sup>30</sup> recently demonstrated small coronary artery tachyphylaxis to continuous intravenous NTG in ischemic dog hearts while the proximal large coronary arteries continued to be responsive to the nitrate. The clinical significance of this observation is far from clear; this experimental model was not designed to evaluate the overall problem of tolerance.

**Human studies** Almost 50 years ago Crindall and co workers<sup>31</sup> investigated tolerance in normal volunteers because of clinical experience suggesting tolerance to nitrates was a common problem in the treatment of hypertension and was an obstacle to successful therapeutic use. They examined tolerance by assessing the headache dose as well as blood pressure and heart rate changes induced by various nitrates. Virtually complete cross tolerance was readily produced among a group of organic nitrates including NTG. Of interest they noted that tolerance to

headache producing action is more easily established than is tolerance to effects on blood pressure and pulse rate.

In 1975 Bernstein and Ivy<sup>32</sup> easily produced tolerance to two long acting nitrates in hypertensive patients. This occurred in 8 to 14 days and disappeared within weeks of cessation of nitrate therapy. Cross tolerance was observed to sublingual NTG used for relief of chest pain in some of these patients who had angina. More recently Schelling and Laigny<sup>33</sup> documented decreased responsiveness to headache and blood pressure-heart rate changes induced by NTG in a group of subjects treated with pentamethyl tetranitrate (PFT) for 4 weeks. This often cited study showed that only partial tolerance was induced by PFT; the response to sublingual NTG was attenuated somewhat but not obliterated. These authors called for improved physician education and further study about the problem of nitrate tolerance.

In order to address the question of cross tolerance to NTG induced by long acting nitrates Zick, Mason and co workers<sup>34</sup> studied arterial and venous vascular tone and blood flow in 12 normal subjects given large doses of ISD. Sublingual NTG resulted in decreased calf vascular resistance and increased calf blood flow as well as an increase in forearm venous volume. Following 6 to 8 weeks of treatment with 120 mg oral ISD daily there was no loss of the arterial response to NTG following sublingual administration of NTG; calf vascular resistance and mean arterial pressure fell to the same extent as the pre ISD measurements. Equivalent vascular responsiveness was also seen after alpha adrenergic blockade and sodium nitrate administration intravenously. However the modest increase (9%) in forearm venous volume produced by NTG was totally blunted after chronic ISD treatment. They concluded that tolerance to venous reactivity induced by ISD readily occurs in the absence of any tolerance to the arteriolar actions of NTG. It should be noted that the venous volume changes in the control state were relatively small. Nevertheless this study is potentially relevant to the use of vasodilator therapy for congestive heart failure. The authors noted that ISD induced headaches disappeared by the fourteenth day again demonstrating the dissociation between the different manifestations of nitrate tolerance.

**Summary** The experience from industrial

exposure to organic nitrates (Monday herd ache, chest pain sudden death) animal studies and data obtained from a variety of clinical investigations into tolerance gives credence to the claim of many clinicians and pharmacologists that the development of nitrate tolerance is a potential hazard in patients chronically treated with long acting nitrates. Most of the documentation of nitrate tolerance in *individual patients* however is anecdotal and provides the weakest link in the argument for tolerance.

#### Evidence that nitrate tolerance and dependence are not major clinical problems

**Clinical experience** While many reviews of nitrate therapy caution physicians about possible tolerance, they do not provide adequate documentation that this is a valid problem in every day clinical practice. Experienced clinicians rarely identify patients who develop tolerance to the benefits of nitrate therapy. The disappearance of NTG headaches is of course an aspect of tolerance that is favorable. Established investigators in the nitrate field virtually never see patients who lose sensitivity to the desired effects of nitrates.<sup>1</sup> A possible case of nitrate dependence was recently reported in a man with severe Prinzmetal's angina and recurrent refractory coronary vasospasm.<sup>2</sup> The patient demonstrated no clinical response to ISD and NTG ointment but had a dramatic reduction in chest pain frequency with the addition of nifedipine, a potent experimental coronary vasodilator. He suffered an acute anteroseptal myocardial infarction 36 hours after withdrawal of long acting nitrates in the hospital. The authors concluded "it seems unlikely that nitrate withdrawal caused a rebound phenomenon since the duration of exposure was far shorter than that of individuals in whom infarction has been reported secondary to withdrawal from industrial exposure to NTG." They speculate that the nitrate withdrawal simply unmasked the intense coronary vasospasm in this patient. It is of interest that the nitrate therapy had been ineffective prior to institution of nifedipine. No definite conclusions regarding NTG dependence can be made from this unusual case.

There are patients with classic angina pectoris who require increasing NTG dosage and/or experience a loss of effectiveness of sublingual NTG.<sup>3</sup> This is generally considered to be accelerating or unstable angina; it is possible that some of these

patients may actually have developed significant nitrate tolerance. There is however no present evidence to support this view. In a recent editorial Zelis and associates state: "Despite decades of acceptance of the reality of nitrate tolerance and despite a firm scientific basis, many seasoned clinicians have had a nagging suspicion that this might be a highly overrated phenomenon. The fear of clinically meaningful nitrate tolerance appears to be unfounded."

**Studies using long acting nitrates in ambulatory patients with angina pectoris** Many studies have demonstrated long term efficacy of various nitrate formulations in angina utilizing chest pain frequency and NTG tablet counts. This type of "soft" data is not ideal to evaluate antianginal therapy; studies producing more valid data utilize serial exercise tests with appropriate controls, placebo groups, crossover trials, etc.<sup>4</sup>

Three recent studies have demonstrated long term angina improvement in patients taking *oral* NTG.<sup>5-7</sup> Using a complex protocol Winsor and Berger<sup>5</sup> concluded that nitrate tachyphylaxis does not occur. According to diary notes and tablet counts over a 24 week period the frequency and severity of angina attacks were significantly decreased in a group of patients taking active oral NTG versus placebo. Possible tolerance was investigated by carefully evaluating the weekly clinical status in patients with angina; none showed a decreased NTG effect over any 11 week period of oral NTG therapy. Serial exercise tests were not performed but treadmill testing revealed improved performance with oral NTG after only 6 to 10 days of therapy. Cole and Kaye<sup>6</sup> documented protracted (6 month) angina protection using the diary method. Using a serial exercise test protocol Davidov and Mroczek<sup>7</sup> repeated treadmill tests at 12 weeks and demonstrated sustained improvement in patients taking sustained action NTG versus placebo orally. Angina frequency was also decreased at 12 weeks in the active drug group.

NTG ointment has also been found to produce sustained relief of angina with no evidence of tolerance to sublingual or topical NTG after 8 to 12 weeks of therapy.<sup>8</sup> NTG ointment caused similar blood pressure and heart rate changes before and after chronic administration and most important repeat challenge with sublingual NTG resulted in identical improvement as well as similar blood pressure and heart rate response. Nevertheless the authors stated that

study is necessary to fully evaluate the problem of tolerance and dependence in patients given physiologically active nitrate formulations. ISD has been given chronically in several studies; tolerance has not been documented. In 1971 the NIH group showed that long term treatment (1 to 7 months) with sublingual ISD (5 to 10 mg q.i.d.) did not attenuate the acute blood pressure, heart rate, or exercise test responses to administered ISD. While questioning whether ISD had truly sustained activity when compared with NTG, these workers have reportedly stated that tachyphylaxis and dependence is not a problem with the usual therapeutic doses of nitrates. Recently an investigation of high dose oral ISD using several exercise tests was reported. Patients were studied with active ISD (40 mg t.i.d.) or placebo before and after 30 days of therapy. ISD resulted in sustained improvement in exercise tolerance and ST depression at 2 and 6 hours after dosing and patients taking active drug showed a significant decreased frequency of anginal attacks and NTG tablet use over the 30 day period. This study clearly demonstrates important physiologic responses to nitrates persisting for at least 30 days of therapy with no evidence of tolerance.

**Studies using long acting nitrates for congestive heart failure.** The utilization of long acting nitrates in the treatment of heart failure has provided further evidence that clinical tolerance to these agents is uncommon. More and more studies are currently being reported assessing the efficacy of unloading therapy in ambulatory patients with heart failure often with higher doses of nitrates than have been used previously. Therefore further evidence regarding this potential problem will be forthcoming. Some preliminary data are already available.

In 1974 Cohn and co-workers reported a case of severe postinfarction heart failure in which only nitroprusside could reverse the deteriorating course. The patient was subsequently given oral ISD and NTG ointment which lowered the left ventricular filling pressure (LVP). He was discharged on large doses of these drugs and had repeat catheterization 10 weeks later which documented appropriate responsiveness to sublingual NTG. Subsequent challenge with placebo instead of ISD resulted in exacerbation of congestive heart failure. After 8 months of chronic nitrate therapy the patient had a smaller heart size and continued to sustain clinical improvement. These

authors treated seven similar ambulatory patients with severe left ventricular failure who "reported improvement in symptoms on vasodilator therapy. No evidence of tolerance was observed. Gray and associates<sup>1</sup> followed nine patients with chronic congestive heart failure on sublingual ISD (5 to 15 mg QID) for 4 to 8 months. All had initially demonstrated acute responses to the drug while in the hospital; cardiac index and venous capacitance increased, while systemic resistance, pulmonary wedge pressure and mean arterial pressure decreased. One patient had follow up hemodynamic evaluation after 2 months of ISD administered on an outpatient basis; further improvement was demonstrated in most parameters. All patients were judged clinically to be improved. They recommended the use of sublingual ISD in the therapy of chronic heart failure. Kovick and associates<sup>2</sup> followed 12 patients with severe congestive heart failure (CHF) on chronic sublingual ISD and oral phenoxybenzamine for a mean of 1 months (range 3 to 21 months). Nine had repeat hemodynamic studies documenting continued improvement in cardiac output, fall in LVP as well as a reduction in echo-derived left ventricular diastolic diameter. At repeat catheterization the patients were given sublingual ISD. Each showed a further reduction in PAV [pulmonary artery wedge pressure] and increase in CI [cardiac index] suggesting that tolerance to the nitrates had not developed. All were clinically improved often with a dramatic decrease in diuretic requirements. Masie and associates<sup>3</sup> used a combination of hydralazine and ISD in six ambulatory patients with severe CHF followed for a mean of 6 months (range 3 to 10 months). One additional patient was given NTG ointment. All seven have shown significant clinical improvement that has persisted for the duration of follow up. Functional class improved in all. One subject was restudied at 8 months and was found to have maintained the vasodilator induced hemodynamic improvement first documented when unloading therapy was instituted during the initial hospitalization. While hydralazine was partially beneficial in these patients, the nitrate therapy clearly was able to reduce LVP. The follow up data do not support the appearance of nitrate tolerance. In a subsequent discussion of these patients the authors comment, "admittedly further studies will be required to document that the hemodynamic effects of these drugs

continue to manifest with their continued use". Addressing the problem of outpatient use of nitrates in congestive heart failure they state "Tolerance to various pharmacologic effects, however may be troublesome during the long term administration of NTG or the other nitrates. It is apparent within a few days and may become of considerable magnitude within two weeks. Fortunately tolerance appears to develop somewhat more readily to nitrate induced headaches than to other pharmacologic effects. This note of caution apparently was not based on any negative clinical experience."

Chandraratna and associates<sup>44</sup> recently reported seven patients with severe biventricular congestive heart failure treated with NTG ointment after first documenting efficacy in the hospital with hemodynamic studies. These patients had considerable clinical improvement at a mean 5-month follow up (range 2 to 12 months) several returning to functional Class I or II. The initial nitrate headaches disappeared or decreased within a few days in all. Follow up hemodynamic measurements were not made. Another report using hydralazine and NTG ointment followed eight Class IV CHF patients for a mean of 5 months after the initial hemodynamic study. All subjects showed subjective improvement with increased exercise capacity. Most had a reduction in cardiac dimensions and a decrease in edema. Functional class improved in all. Less dramatic results were seen in a series of nine left ventricular failure patients followed for a mean of 11 months (range 1 to 14 months) who received high dose chewable ISD plus hydralazine.<sup>45</sup> The regimen was well tolerated but objective evidence for improvement was limited. Tolerance was not recognized. The same group more recently reported the first controlled trial of chronic unloading therapy in CHF.<sup>46</sup> Sixteen patients were randomized to ISD (40 mg orally q.i.d.) or placebo in a double blind 16-week crossover study. Only six patients were able to complete the entire protocol. The nitrate group had significantly less "complicating events" (7/85 versus 17/76) and most were clearly benefited when compared to the placebo group. No patient deteriorated on ISD while the condition of five placebo treated patients worsened. Exercise tolerance increased in the ISD group but half the placebo group also showed improved exercise performance. Other objective evidence for improvement (physical examination, chest x-ray, echo dimensions, car-

diac output) were no different in the ISD or placebo groups. The authors conclude that nitrate therapy resulted in symptomatic clinical improvement but long term prognosis could not be assessed. They did not find evidence of ISD tolerance. However the possibility of nitrate dependence was raised in this study because of the disturbing number of clinical events (including two sudden deaths) in those patients with underlying ischemic heart disease who had been taking ISD prior to study and then discontinued the drug during the 4 week placebo run in period. Most "events" were worsening heart failure but the two deaths suggest a possible nitrate withdrawal effect similar to that seen in industrial workers exposed to NTG. Most of these patients had been taking nitrates for less than 2 weeks and the numbers are small. Thus further study of the possibility of nitrate dependence in this type of patient seems warranted.

Studies designed to evaluate nitrate tolerance. Aronow and Chesluk<sup>47</sup> treated patients with angina for 4 weeks with sublingual ISD and then assessed their response to sublingual NTG. Exercise improvement was seen following sublingual NTG administration in the subjects taking ISD or placebo with no suggestion of ISD induced attenuation to the NTG. As already cited workers at the National Institutes of Health evaluated nitrate tolerance in patients receiving chronic ISD as well as topical NTG and found no loss of responsiveness to sublingual NTG or to the long acting nitrate that had been given for the duration of the study. In the ISD study the response to acute ISD and sublingual NTG was evaluated by treadmill testing after 10 days of ISD in six patients and 1 to 7 months in another four patients. Six subjects using NTG ointment were retested after 6 to 8 weeks of chronic therapy. A patient was reported in 1971 who had taken oral ISD for 4 months and showed no tachyphylaxis to the drug's effect on improving exercise tolerance. In a study measuring digital pneumoplethysmographic responses to nitrates it was shown that 1 week of treatment with oral sustained release NTG (5 mg b.i.d.) did not alter the mean group response to the drug. The methodology and statistical analysis in this study leave much to be desired.

Two well-designed studies to evaluate the problem of tolerance and cross tolerance to high-dose ISD in patients with stable angina pectoris were recently reported.<sup>48</sup> Danahy and Aronow<sup>48</sup>

followed 19 patients on oral ISD for 3 to 10 months. The dose of ISD ranged from 10 to 50 mg q.i.d. (average dose 27 mg). Responses to sublingual NTG and oral ISD were assessed by measurements of blood pressure, heart rate and bicycle exercise performance up to 5 hours and were compared with similar measurements made prior to chronic nitrate treatment. The improvement in exercise tolerance with NTG and ISD was similar during both evaluations. Oral ISD produced sustained improvement in exercise performance at 1 and 3 hours but not at 5 hours before and after chronic use of the drug. The ST segment responses to exercise were unchanged after ISD treatment. Patients reported no decrease in the therapeutic benefit from sublingual NTG while taking high dose ISD. However, blood pressure and heart rate responses to ISD were attenuated after chronic treatment with this drug. The mean decrease in systolic blood pressure and increase in heart rate on the post ISD treatment evaluation were less than pre ISD therapy; the mean group responses were decreased at all testing periods up to 5 hours after oral ISD. Thus, the hemodynamic responses to an acute challenge with oral ISD were blunted as measured by blood pressure and heart rate, but the antianginal efficacy of both sublingual NTG and oral ISD were unaltered following long term ISD administration. This clearly suggests differential tolerance

the various nitrate actions as has been noted in her studies. Headaches induced by ISD were common but were absent or less severe in most subjects after 2 to 3 weeks of therapy again indicating partial ISD tolerance. The discrepancy between the clinical and hemodynamic effects of chronic ISD was unaccounted for and the authors concluded: "We could detect no evidence of development of tolerance to the antianginal effect of the drug. Similarly, sublingual NTG remains effective after chronic use of ISD."

In another similar study to investigate the problem of cross tolerance to ISD, 28 patients with stable angina pectoris were given high dose oral ISD (120 mg daily) for a month.<sup>3</sup> Peak exercise performance was measured as well as the exercise response to acute sublingual NTG administration. The patients were able to respond maximally to sublingual NTG after chronic ISD treatment and showed increases in exercise duration and maximal oxygen consumption equivalent to the pre ISD measurements. The ISD group also demonstrated greater pre-NTG exer-

cise capability than prior to the 4 weeks of treatment. Exercise induced ST depression decreased in the ISD group; administration of sublingual NTG produced no further reduction in the ischemic EKG response. The data strongly suggest that tolerance to ISD itself did not develop. Although the actual magnitude of NTG induced exercise improvement was less than in the placebo group following 1 month of ISD administration, the authors emphasize that the ISD treated patients had already showed objective improvement prior to the administration of sublingual NTG and the maximal response following NTG was similar to that before treatment. They conclude: "cross tolerance to the antianginal effect of sublingually administered NTG is not induced by long term oral administration of ISD."

The most recent report available is that of Franciosa and Cohn<sup>4</sup> who used high-dose oral ISD (160 mg daily) for vasodilator therapy in CHF. In a study designed to examine the possibility of tolerance, they reevaluated 11 patients with right heart catheterization after 3 months of treatment with ISD or placebo. The nitrate group showed a slightly lower baseline LVFP and continued to lower this pressure 90 minutes after acute ISD administration; mean arterial pressure also fell in the ISD treated patients. This study demonstrated sustained hemodynamic reactivity to the nitrate after prolonged high dose ISD therapy and does not support the appearance of ISD induced tolerance.

## Conclusions

1. There is little evidence that chronic administration of organic nitrates, even in large doses, induces clinically important tolerance or cross tolerance to NTG or other nitrates in patients being treated for angina pectoris or heart failure. Recent well designed studies demonstrate the persistence of undiminished therapeutic activity in response to nitrate administration in patients treated with long acting nitrates for periods of 1 to 10 months. Some attenuation of venous and arterial vasodilation following long term ISD therapy has been noted and is of uncertain clinical significance. The experience from the explosives and NTG manufacturing industries as well as the results of a number of earlier animal and human studies clearly demonstrate that nitrate tolerance and cross tolerance can occur and often with dramatic speed. Thus, the possibility of

clinical tolerance must be kept in mind in the treatment of patients with long term nitrate therapy

2 Nitrate therapy for angina or heart failure should be judiciously initiated and thoughtfully maintained. The lowest effective dosage should be utilized. Individual sensitivity to nitrate action is highly variable and totally unpredictable. Because the experience with high dose nitrate administration is relatively new, evidence for tolerance should be especially sought in patients receiving such therapy and periodic reassessment of the nitrate's efficacy should be made. Earlier investigations suggest that nitrate tolerance is more likely and more quickly induced with high doses.

3 The most serious problem of nitrate dependence is as yet unresolved. Death, myocardial infarction and chest pain syndromes have been amply documented in industrial employees exposed to NTG and nitroglycerin who leave the work environment for several days. Coronary spasm has been shown to occur in some of these individuals. The recent report of Franciosa and co-workers<sup>11</sup> again raises the specter of nitrate dependence, but the patient population is too small and the experience too limited to draw any firm conclusions. Although unlikely withdrawal syndromes may become a real clinical problem, particularly in patients treated with high doses of nitrates, similar reports have been recently described in propranolol therapy for angina pectoris<sup>12</sup> many years after beta blockers were introduced for angina. It seems prudent to carefully taper nitrate therapy in patients with proven coronary atherosclerosis who have been on chronic long acting nitrate regimens if the drug must be stopped. These patients should be admonished to watch for symptoms of increased chest pain during the withdrawal period or when they discontinue their medication inadvertently. The majority of studies reviewed in this report were designed to examine tolerance rather than dependence. Further experience is necessary before the question of nitrate dependence can be fully answered.

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# Clinical pharmacology of the new beta-adrenergic blocking drugs Part 9 Nadolol A new long-acting beta-adrenoceptor blocking drug

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The value of beta adrenergic blockade in arterial hypertension, angina pectoris and arrhythmias has been well established during the last decade.<sup>1</sup> An increasing number of beta blockers with varying pharmacodynamic and pharmacokinetic properties have recently been introduced into clinical practice.

Nadolol (SQ 11270) is a new non cardioselective beta adrenergic blocking agent which was developed in the United States. It has a unique pharmacological property in that it has the longest plasma half life of any known beta blocking drug and can be administered once daily.<sup>2</sup>

The clinical experience with nadolol is now being gathered world wide in angina pectoris, arrhythmias and hypertension. The first clinical trial using nadolol for the treatment of hypertension and angina pectoris. In this article the clinical pharmacology, efficacy and toxicity of this promising new agent will be described and its potential therapeutic applications will be discussed.

## Pharmacodynamic and pharmacokinetic properties (Table I)

Nadolol, 2,3,4,5-tetrahydro-5-[(2-hydroxy-1-tert-butylamino)propoxy]-2,3-naphthalenediol (Fig 1) is a non-selective  $\beta$  adrenoceptor

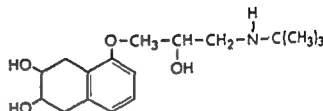


Fig 1 Structural formula of the  $\beta$  adrenoceptor blocking drug nadolol

blocking drug which lacks both membrane stabilizing and intrinsic sympathomimetic activity (partial agonist activity).<sup>3</sup> It has a level of potency which is two to four times that of propranolol.<sup>2</sup> Compared to propranolol nadolol (probably related to its lack of membrane stabilizing effect) has been found to be approximately 50 to 500 times less depressant (contractility) to the isolated guinea pig atrium.<sup>4</sup>

Nadolol is absorbed rapidly from the gastrointestinal tract achieving its peak effect in 3 to 4 hours.<sup>5</sup> Only 30% of the oral dose is absorbed. The drug is not metabolized in the body and is excreted unchanged in the urine (70% of absorbed dose) and via the bile in the feces (20% of absorbed dose).<sup>6,7</sup> Nadolol is 30% bound to plasma proteins.<sup>2</sup> The drug has a plasma half life of 17 to 23 hours the longest of any known beta blocker.<sup>2</sup> The plasma half life is even longer where there is renal dysfunction with elimination proportional to creatinine clearance. The drug can be removed with hemodialysis.

## Physiological and metabolic effects (Table II)

The hemodynamic effects of nadolol are attributable to  $\beta$  adrenoceptor blockade. In human

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Table I Pharmacological properties A comparison between propranolol and nadolol

Pharmacologic property	Propranolol	Nadolol
Beta blockade potency ratio (propranolol = 1)	1	2-4
Cardioselectivity	0	0
Partial agonist activity	0	0
Membrane stabilizing activity	+	0
Extent of absorption (% of oral dose)	>90	≈30
First pass hepatic metabolism	+	0
Protein binding (%)	≈90	≈30
Elimination half life (hours)	3.5-6	17-24
Urinary and fecal recovery of unchanged drug (% of oral dose)	<1	>90
Active metabolites	+	0

Table II Hemodynamic and electrophysiologic effects of propranolol and nadolol\*

Hemodynamic parameter	Propranolol	Nadolol
Resting heart rate	↓	↓
Exercise induced increment in heart rate	↓	↓
Peripheral resistance	↔	↔
Effect on blood pressure (rest)	↓	↓
Exercise induced increment in blood pressure	↓	↓
Cardiac contractility	↓	↓
Cardiac output	↓	↓
Effect on elevated plasma renin	↓	↓
Effect on atrioventricular conduction	↓	↓

In dosages giving similar degree of beta blockade

studies nadolol like propranolol reduces cardiac contractility and work. In a hemodynamic study of 14 patients with coronary artery disease both nadolol and propranolol (in similar beta blocking doses) reduced heart rate, cardiac index, stroke work, ejection fraction,  $dp/dt$  and  $V_{max}$ ; peripheral resistance rose slightly.<sup>8</sup> The cardiocirculatory effects of nadolol and propranolol were similar. In another study employing radionucleotide techniques to evaluate left ventricular function in patients with coronary artery disease both nadolol and propranolol (in equivalent beta blocking concentrations) reduced the ejection fraction.<sup>9</sup>

The findings of the above studies differ from the results of animal experiments where nadolol was found to have less myocardial depressing effect than propranolol. These experiments were done in the isolated guinea pig atria and the membrane stabilizing action of propranolol may have been important with the concentrations of drug used.<sup>1</sup>

In several experimental studies nadolol has been demonstrated to be effective against cardiac

arrhythmias.<sup>1</sup> As seen with other beta blocking agents, this antiarrhythmic activity appears to be related to  $\beta$  adrenergic receptor blockade, an action that would antagonize the capacity of catecholamines to induce arrhythmias by alteration of cardiac automaticity and conductivity.<sup>11</sup>

Nadolol was effective in antagonizing ectopic activity occurring during vagal induced depression of primary pacemaker activity, presumably by inhibiting the actions of catecholamines on the automaticity of the ectopic pacemaker. Both nadolol and propranolol antagonized isoproterenol induced tachycardia and ouabain induced arrhythmias in cats. The two agents also antagonized coronary artery ligation induced ventricular fibrillation. In contrast to propranolol, nadolol was considerably weaker in suppressing existing digoxin induced arrhythmias and lacked membrane stabilizing activity. Both nadolol and propranolol depress atrioventricular conduction. The duration of beta blocker effect was five times greater with nadolol than with propranolol.<sup>1</sup>

Nadolol has been shown to have similar effects on glucose and lipid metabolism as propranolol.<sup>13</sup> With regards to other physiologic parameters (effects on the bronchial tree, platelet function, hemoglobin oxygen dissociation) there is insufficient data.

Nadolol has been shown both in animal experiments and in human trials to lower pretreatment plasma renin activity as much as 50%.<sup>14</sup> This decrease in plasma renin activity is in the same range as earlier reported for hypertensive patients treated with propranolol. In preliminary studies (animal and human) nadolol has been shown to increase renal blood flow. This finding contrasts with the observations made with all other beta blocking drugs where renal blood flow has been shown to decrease due to decreased cardiac output. The mechanism for this paradoxical renal blood flow effect with nadolol has not been elucidated.

#### Therapeutic applications and clinical experience

The hemodynamic and pharmacokinetic profile of action of nadolol suggested its application in cardiovascular disorders such as hypertension,<sup>15</sup> ischemic heart disease, and cardiac arrhythmias.

**Hypertension** It is well recognized that beta adrenergic blocking agents are effective in controlling the blood pressure of many patients with hypertension. As mentioned previously, there is no consensus of opinion as to the mechanism or mechanisms by which these drugs lower blood pressure. Moreover, there appears to be no difference in therapeutic efficacy between the different beta blockers (with a similar degree of  $\beta$  blockade) in hypertension.<sup>16</sup>

Nadolol has proven to be a safe and effective antihypertensive agent when compared with placebo. A preliminary, single blind study was carried out with nadolol in 20 untreated patients with essential hypertension. After a 2 week period on placebo, patients were treated for 14 weeks with daily doses of 40 mg nadolol (20 mg twice daily). Dosage was increased every second week up to a maximum of 560 mg daily until the patient was stabilized at an effective normotensive dose level. Compared to placebo, there was a significant reduction in both systolic and diastolic blood pressure (approximately 24/21 mm Hg) at an average daily dose of 110 mg nadolol. Pretreatment plasma renin activity value decreased

by 50% as a result of 14 weeks treatment with nadolol. This decrease in plasma renin activity is in the same range as earlier reported for hypertensive patients treated with propranolol. Apart from a tendency to bradycardia, no other side effects were reported.

The long half life of nadolol in serum suggested the possibility of administering the drug only once a day. Many trials are currently in progress comparing the efficacy of oral nadolol administered once daily with propranolol administered four times daily.

A drug which can be taken once daily could enhance patient compliance in the treatment of hypertension. Studies have shown that patient compliance in hypertension varies with the complexity of the dosing regimen.<sup>17</sup> In one large study of a hypertensive population, only 5% of patients given a diuretic failed to take the prescribed dose (once a day regimen) presumably due to the simple therapeutic regimen, whereas the proportion not taking alpha-methyldopa, propranolol, and reserpine (multiple dose regimen) approached 30%.<sup>18</sup> This lack of patient compliance was unrelated to side effects.

Would a beta blocking drug with a 24 hour half life therefore be an advantage in the therapy of hypertension? Propranolol and oxprenolol have comparatively short half-lives, and if this alone determined the frequency of drug dosage, these agents would need to be given at least four times daily. However, the physiological effect of beta blockade upon blood pressure substantially outlasts the survival of unchanged drug in the plasma, twice or even once daily dosage seems adequate.<sup>19,20</sup> Therefore, preparations with a long pharmacokinetic half life such as nadolol, atenolol, or slow release preparations of drugs such as oxprenolol may confer no great advantage.

**Angina pectoris** Multiple studies have demonstrated the effectiveness of beta adrenoceptor blocking agents for the treatment of patients with angina pectoris. As described previously, these drugs reduce the determinants of myocardial oxygen consumption, enabling a patient to do more work.<sup>21,22</sup>

A randomized double blind study was carried out in 24 patients with stable angina pectoris to compare the efficacy of nadolol and propranolol.<sup>23</sup> After a period on placebo, 14 patients received nadolol once daily and 10 patients received

propranolol four times daily over a 10 week dose finding period followed by a maintenance period of 4 weeks. The optimal daily dosage for nadolol was 100 mg and 112 mg for propranolol. The parameters used for evaluation of therapeutic effectiveness included the number of anginal attacks, number of nitroglycerin tablets needed, time before onset of chest pain during an exercise test, exercise time and over all clinical impression. Nadolol and propranolol were equally effective in reducing anginal attacks and nitroglycerin consumption. Similarly, exercise tolerance was improved with both drugs.

It was concluded from this study that nadolol once a day is as effective as propranolol four times daily in treating patients with angina pectoris.

A beta blocker that can be given just as a single daily dose for angina pectoris might be a factor of major importance in ensuring patient compliance. What is not known at this time, however, is whether other beta blockers with shorter half-lives can also be given once or twice daily for angina pectoris.

A larger multicenter trial in this country comparing nadolol once daily with placebo and propranolol taken four times daily has been completed. The published results are being awaited with great interest.

**Arrhythmias** Nadolol has been shown to be an effective treatment for cardiac arrhythmias. As demonstrated with all beta adrenoceptor blocking drugs, its antiarrhythmic properties stem from the ability to antagonize the effects of catecholamines on cardiac automaticity and conductivity.

Nadolol was initially developed as an antiarrhythmic agent in 1973. Although the electrophysiological properties of the drug are well known, there is no large clinical data base to date.

In one study, 29 patients with frequent ventricular and supraventricular ectopic beats and other supraventricular arrhythmias received sequential doses of placebo and nadolol. Dose titration and nadolol maintenance were accomplished during a four week period on doses up to 100 mg/day, preceded and followed by placebo periods extending to two weeks. Ectopic activity was monitored by Holter 24 hour dynamic electrocardiography. A reduction or remission of arrhythmia was observed in approximately two thirds of patients. Arrhythmias that responded favorably involved

ventricular bigeminy; paroxysmal atrial tachycardia and sinus tachycardia. Patients with atrial flutter or fibrillation did not convert to normal sinus rhythm, however, all patients had a favorable reduction in ventricular response. Maintenance doses most frequently used were 60 to 160 mg/day in single or divided doses. Reductions in resting heart rate and arterial pressure consistent with beta adrenoceptor blockade were observed. It was concluded from this trial that nadolol might be of value in the treatment of cardiac dysrhythmias.

A beta adrenoceptor blocking agent with a long half-life that can be administered to patients once daily for management of cardiac arrhythmias might prove extremely useful in clinical practice. Trials with nadolol in one daily dose compared with other beta blockers and other antiarrhythmic agents are still necessary for evaluating the agent in the acute and chronic treatment of patients with cardiac dysrhythmias.

#### Side effects and toxicity

In the limited clinical experience to date, nadolol has side effects similar to other beta adrenoceptor blocking drugs (i.e. propranolol).<sup>14</sup> No unusual toxic effects have been demonstrated and carcinogenicity study requirements have been met.

One potential problem with chronic nadolol administration might be the toxic accumulation of drug in the plasma of patients with impaired renal function. With its long half-life, lack of hepatic metabolism and renal elimination properties, nadolol dosage must be varied according to the serum creatinine.<sup>6</sup> In situations where toxic levels of the drug might accumulate, the drug is dialyzable.

#### Therapeutic implications and conclusions

Nadolol is an effective beta adrenoceptor blocking agent with the longest half-life among the compounds of this class. This property would enable the drug to be administered once daily and clinical studies have substantiated the effectiveness of this regimen. With the common problem of patient compliance daily in hypertension, arrhythmia and angina pectoris where multidose regimens are used, an agent which can be taken once daily would provide a major advantage.

On the other hand, recent studies have suggested that the beta adrenoceptor bl

drugs with short half lives have longer pharmacodynamic actions which might obviate the need for their frequent dosing

Until this crucial pharmacological issue is resolved nadolol appears to be an important pharmacological advance

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## Annotations

### The Canadian trial of aspirin and sulfipyrazone in threatened stroke

There is good evidence that in a large percentage of patients with transient focal cerebral ischemic attacks (TIAs) platelet fibrin emboli are dislodged from an atherosclerotic ulcerative and stenotic lesion in a major cervical artery and then occlude one or more intracranial or retinal arteries. Data from a community study of TIA indicate that the peak period of stroke occurrence is within the first few months following the onset of TIA.

Endarterectomy which is applicable primarily to patients with carotid TIA is aimed at eliminating the lesion which allows accumulation of platelet fibrin material. Anticoagulant treatment should prevent formation of fibrin that maintains the stability of a beginning platelet thrombus. Antiplatelet drugs may prevent platelet aggregation or more importantly should prevent adherence of platelets to an area of endothelial injury.

The Canadian trial of antiplatelet drug in "threatened stroke" is a well designed study and there are few important faults with the methodology described in the publication. It is important to note that there were almost as many patients excluded from the study as were randomized and this raises questions about whether the group randomized was representative of TIA in general. It is also relevant that 46% of the patients included had neurologic residua at the time of entry into the study—strictly speaking these patients had small cerebral infarcts not TIA. We simply do not have data on whether strokes of that type are comparable to TIA.

The number of months between the first TIA and randomization was similar in each group studied and this is important because the greatest risk of stroke is soon after the onset of TIA. There were 34% over age 70 among patients not treated with either drug in contrast to about 15% in the other three groups. This may seem to be a bias against those untreated patients; however the fact of occurrence of TIA in a patient greatly overrides the effect of age in regard to stroke probability so that weighting may not be important.

One of the objectives of the Canadian trial of aspirin and sulfipyrazone in patients with TIA was to determine in four groups of patients whether aspirin, sulfipyrazone or both would reduce the occurrence of first stroke or recurrent stroke when compared to an untreated group. If one compares those four groups independently the study did not show a difference among the four groups. Table V of the publication assuming that the patient months of observation are similar indicates that among the patients treated with a *purin* alone there were 23 strokes and among those that received no treatment there were 20 strokes. Among the men who received a *purin* alone there were 14 strokes and there were 15 strokes among those men who received no treatment.

The publication emphasizes the combination of stroke plus death as endpoints for combinations of the four groups of patients. However there is an important problem with that

approach. Among patients with TIA only about 20% of deaths are due to stroke; nearly 50% are due to heart disease and 25% to other causes most of which are nonvascular. The approach used by these investigators, in effect aims to assess stroke plus death due to heart disease or at least heavily weighted for heart disease. There would be no argument if the analysis was concerned only with mortality but that would be a hopeless proposition for comparison nor would there be argument with the assessment of all strokes and all cardiac events without regard to death. In the latter circumstance if the pathophysiology is different for the different types of endpoints, and that is a possibility, a beneficial effect in regard to stroke could be masked.

It is feasible to assess the effect on stroke occurrence exclusive of other considerations. This may be done by constructing a table comparable to a mortality table or the complement of a life table and using actuarial analysis with stroke as the endpoint rather than death. Each interval assessed determines the probability of stroke (with or without death) by the number of persons who have had a stroke in the interval divided by the number of persons under observation times 100.

When a person is lost to follow up or is withdrawn for any reason that person is removed from the denominator of the fraction. Those who die from a cause other than stroke are no longer at risk for stroke so are also removed from the denominator or from those under observation but are not counted as endpoints. Of course this is not a real life situation and one cannot ignore the risk of death in a drug trial but that can be assessed separately. This technique does allow a time-based judgement of the effect on stroke exclusive of other disorders affecting the study population. This type of actuarial analysis has been used for other studies of the effect of treatment on stroke occurrence.

Table IV in the Canadian study shows the results in the four groups of patients. The expected number of events was determined by a proportional share of all events among the patients. Assuming that the patient months of observation were similar in the *a. purin* groups and the *non aspirin* groups, one can calculate from the data that there was approximately a 25% reduction in stroke among those taking a *purin*. However that difference is not significant. For males there was a 45% reduction which was significant; however it is not appropriate to examine subgroups for significance when the overall comparison is not significant. If one analyzes the many variables involved in the subgroups, it should result in 1 out of 20 being significant on the basis of chance alone. The observed difference between men and women is intriguing and does deserve further study.

The graph in Fig. 1 from the publication shows the kind of cumulative probability of stroke analysis to which I previously referred but this also includes death. The discordant group



in the one which included men who were on a purin plus sulfinpyrazone so at least in males the two drugs may be more beneficial than either one alone.

There are no data which allow satisfactory comparison of carotid endarterectomy, anticoagulant therapy and antiplatelet therapy for treatment of TIA. The probability of stroke for a normal population age 65 to 74 years is about 1% per year. When TIAs have been present for more than several months the probability of stroke is about 6% per year without treatment. The extracranial occlusive disease study indicated that the probability of stroke was about 3.5% per year following surgery, but if the surgical morbidity was excluded it was less than 2% per year. Among all of the anticoagulant studies of the treatment of TIA controlled and uncontrolled, the highest annual stroke rate noted is 3% per year and that figure came from a population study which began at the onset of TIA. Taking the observations of the Canadian study literally, the probability of stroke in men taking a purin was in excess of 5% per year and in women was greater than 6% per year. For men taking a purin and sulfinpyrazone, the stroke probability was greater than 2% per year.

These probabilities of stroke cannot be directly compared as there is no way to assess whether the different groups studied were in any way comparable. It is clear that patients with TIA have a greatly increased risk of stroke compared to a normal population but it is difficult to establish with certainty a difference in stroke probability based on the effects of various types of treatment that have been proposed.

Our preference for treatment of TIA at present is surgical if an appropriate carotid lesion is present but that must presume a surgical experience with not much over 1% combined stroke morbidity and mortality. If surgical treatment is not appropriate, anticoagulant treatment is preferred at the onset of TIA for the first few months when there appears to be the greatest benefit with the least risk. Since

there may be a modest benefit from a purin treatment we recommend treatment with aspirin after the cessation of anticoagulant therapy and then discontinuation of the aspirin at one year after the onset of TIA unless there is recurrence of symptoms.

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## Excessive proneness of Jews to ischemic heart and bowel diseases

Abu Zeid and co workers have recently reported on ethnic differences in mortality from ischemic heart disease, a study of migrant and native populations—observations related to Manitoba for the period 1960 to 1969. It transpired that a much higher risk of mortality than the expected was found among Canadian born Jews. The disparity was much more marked for males than for females. The standardized mortality (ICD rubric 420) ratio for males was 166/3. This figure was by far the highest of the 2 ethnic male populations studied, and indicated a mortality rate far in the disease among the highest yet reported. This much higher than average mortality rate in Canadian born male Jews confirms earlier observations made in New York in 1951 which revealed that manifest ischemic heart disease (IHD) in a Jewish male group was double that found in an Italian male group.

In Johannesburg, South Africa, in 1960 the ratio of crude mortality rate from IHD (ICD rubric 420) for non-Jewish compared with Jewish males was 1:1.5. Later in 1972 the corresponding ratio was 1:1.71. For the roughly 380,000 non-Jews and 60,000 Jews (both sexes) in Johannesburg, crude non-standardized death rates from IHD were roughly 270 and 3.0 per 100,000 respectively. IHD was responsible for approximately 22 and 37% respectively of all deaths of non-Jews and Jews. As a comparison it is highly illuminating to note that in Tel Aviv, Israel, in 1974 IHD was reported as being responsible for 38% of all deaths.

In Scotland a very high mortality rate from IHD is associated with a very high mortality rate from colon cancer. It is therefore important to note that the crude colon cancer mortality rate for Johannesburg Jews (males and

females combined) for the period 1968 to 1972 was found to be (1) double that of non-Jewish Whites and (2) four times that for the population of Israel. Differences in values between the sexes was slight. The rate for total Johannesburg Jews was 20 per 100 000, the same as that for the population of Scotland for the same period—whose rate was the highest of values reported for national populations. Remarkably no such disparities prevailed for rectal cancer. Furthermore a recent survey has indicated that the prevalence of ulcerative colitis (a risk factor for colon cancer) in Johannesburg Jews is more than double that prevailing for the non-Jewish White moiety. A report from Baltimore indicated the corresponding differential to be even greater.

Our preliminary dietary studies by one of us (C H) on groups of Jews in Tel Aviv and in Johannesburg have indicated no outstanding differences in average intakes of gross dietary components although in the Johannesburg group greater proportions of the fat and protein moieties are derived from animal sources. However undoubtedly there were greater disparities in dietary patterns 10 to 20 years ago.

Finally there is evidence that for Jews in the USA expectation of life at 65 years is decreasing, in contrast to that of most other populations.

We certainly would not wish to unduly press the accuracy of our data; nevertheless the very excessive proneness of Johannesburg Jews to the diseases mentioned is judged to be beyond dispute.

We very much doubt whether the phenomena are explicable wholly on the basis of differences in environmental factors, particularly diet. We consider that not only individuals but ethnic groups such as Jews may be programmed with the weaknesses described which becomes more prominent with rise in sophistication of diet and manner of life. It may be recalled that Burch entertained the possibility that Negroes in the USA may be programmed for an expectation of life shorter than that of the White inhabitants.

It would seem very important that in cities or regions where major differentials in morbidity and mortality from particular diseases prevail between Jewish and non-Jewish Whites, there should be intensive characterizations of diet and biological variables. It should then be possible to learn *inter alia* to

what extent similarities in these variables evoke or are consistent with differences in pathology.

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## The clinical value of cardiac fluoroscopy

In 1962 Ench Zdansky wrote in his famous classical work 'Roentgen diagnosis of the heart and great vessels' (Roentgen diagnosis of the heart and great vessels). Even today thorough fluoroscopy is an integral part of the roentgenologic examination of the heart and great vessels. For a long time fluoroscopy was a powerful tool in the hand of the cardiovascular radiologists and cardiologists for the evaluation of the cardiac chambers and great vessels.

In the last 20 years reliable electrocardiographic criteria for hypertrophy and dilatation of the heart chambers were developed. More recently ultrasonography was introduced as a valuable diagnostic tool in the diagnosis of various abnormal

heart conditions. Cinefluorography has become another new modality in the diagnosis of heart diseases. Considering these new developments it appears appropriate to review the role of conventional fluoroscopy in differential diagnosis of the heart diseases.

In our experience the standard four views of the chest with barium swallow obtained preferably with high kV technique have replaced fluoroscopy in the evaluation of cardiac chamber enlargement. On good films the heart is seen without magnification and its configuration can be determined. Correlation between pulmonary vascularity and shape can be readily made. The

of the pulmonary artery by fluoroscopy is highly subjective and the so-called typical hilar dance is rarely observed.

The patient's radiation exposure is 4 to 100 times greater for one minute of fluoroscopy than for a single I.A. chest radiogram. Thus fluoroscopy represents a significantly higher radiation hazard which is particularly important in the pediatric age group. However, there remain some indications for cardiac fluoroscopy which should no longer be performed on a routine basis.

If valvar calcifications are to be demonstrated fluoroscopy or preferably cinefluorography is the procedure of choice. But nowadays the same diagnosis can be made without ionizing radiation, namely by ultrasonography. However, small coronary artery calcifications are detectable only during fluoroscopy. In both groups of patients fluoroscopy does not have to be performed as a separate procedure. Most of these patients came to cardiac catheterization or coronary arteriography and thus calcifications can be seen on the angiographic studies.

The function of the artificial prosthetic valves can be well studied by fluoroscopy or preferably by cineradiography. For the visualization of the movement of artificial discs and valve leaflets a C-arm is very helpful because a true end-on view has to be obtained for the detection of these extremely thin structures. Admittedly, similar information can be obtained nowadays by two dimensional ultrasonography.

Fluoroscopic evaluation of ventricular aneurysms is not indicated. Paradoxical pulsations are virtually never seen.

Akinetic areas are usually not appreciated. Aneurysms or contraction abnormalities can only be excluded with certainty by cine left ventriculography. Transmitted pulsations cannot be distinguished from true pulsation. This is the reason why fluoroscopy does not allow differentiation of mediastinal masses from aortic aneurysms.

The diagnosis of pericardial effusion used to be a good indication for fluoroscopy. In recent years however it was replaced by ultrasonography which is much more sensitive.

In summary, few indications remain. Cardiac fluoroscopy has been largely replaced by better and more diagnostic less hazardous tests. In carefully selected patients it remains a useful diagnostic tool but its indiscriminate and routine use is no longer justified.

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## Of T waves and chronic congestive heart failure

Chronic congestive heart failure (CHF) is always associated with T wave abnormalities in the electrocardiogram. Abnormal T waves are a reliable diagnostic confirmation of chronic CHF. Beware of a diagnosis of chronic CHF in the absence of abnormal T waves in the ECG.

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## Surgical closure of coronary artery fistula emptying into left ventricle

### To the Editor

We read with interest Drs Arani, Greene and Klocke's report on coronary artery fistulas emptying into left heart chambers. We recently reported a case in which the fistula was surgically closed and presented a movie of same at the American Heart Association meeting in Anaheim California on November 17, 1975 and at the American College of Chest Physicians meeting in Washington D.C. on November 19, 1978. Our patient's fistula involved the main left anterior descending coronary artery and not a diagonal or contributing branch. We congratulate the authors on their report but must point out that a more careful perusal of the recent surgical literature would have discovered our recent contribution to the understanding of this interesting anomaly.

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### Reply

#### To the Editor

Although Dr. Midell's and Dr. Bermudez's abstract regarding a case of coronary fistula emptying into the left ventricle was presented earlier, their paper was published in August 1977, while our paper on coronary artery fistula emptying into the left heart chamber was submitted for publication in September 1977. We congratulate the authors for their successful closure of the left anterior descending-left ventricular fistula but would like to point out that in our case the fistula consists of a diagonal branch emptying into the left ventricle with a small shunt and in our judgment the risk of surgery outweighs the benefits.

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## Single daily dosing of propranolol in hypertension

### To the Editor

In the treatment of hypertension perhaps the most difficult problem is patient medication compliance. Since one reason for poor compliance is complex medication scheduling, simplification of the therapeutic regimen should help improve compliance. Although propranolol was originally recommended to be given in four doses daily (twice daily dosing in the treatment of hypertension is now approved in the United States), single daily dosing of propranolol has been studied and appears safe and effective. To our knowledge, however, there are no published American trials of single daily dosing of propranolol in hypertension. The current experimental investigation was conducted in an effort to provide further information on the feasibility of administering propranolol in a single daily dose.

Seven patients (one female, six males) with confirmed essential hypertension whose average diastolic blood pressure taken on three consecutive visits was  $> 90$  mm. Hg and who were subsequently controlled with propranolol, were included in the study. The disappearance of sound (the fifth Korotkoff phase) was used as an indication of diastolic blood pressure. Average age was 50 years (range 20 to 61 years) and average daily dose of propranolol was 183 mg (range 40 to 320 mg). All patients were concurrently on a diuretic (six patients on hydrochlorothiazide, one patient on furosemide). With the exception of one patient who was also treated with prazosin, 2 mg/day, no other antihypertensives were given. No drugs or dosages were changed during the study and no patient who had a contraindication or relative contraindication to the use of propranolol was included in the study.

After the nature and purpose of the study were explained and informed consent was obtained, the patients were stabilized on twice daily doses of propranolol and were instructed to take their dose at 9 A.M. and 9 P.M. daily, omitting their A.M. dose on study days. Every two weeks for eight weeks, blood pressure in the sitting, standing, and supine positions along with heart rate were recorded at 9 A.M., 12 hours after the last dose of propranolol. Three minutes was allowed between each postural change. At the end of eight weeks, the patients' total daily dose of propranolol was given as one dose. After blood pressure and heart rate were recorded, the propranolol was administered by the investigator at 9 A.M. with measurements recorded again two hours later (to reflect the approximate peak plasma concentration). Patients were then seen every two weeks for eight weeks with recordings taken 24 hours after the last dose (9 A.M.) and two hours later. At each clinic visit the patients were questioned about possible adverse effects. Mean blood pressures on twice daily and once daily therapy were compared using the Student's *t* test for dependent observations.

Mean systolic and diastolic blood pressures and heart rates are given for each regimen (Table 1). Statistical comparison showed that blood pressure changes between twice daily

Table 1 Antihypertensive effects of single daily dosing vs twice daily dosing of propranolol

	Mean BPS (mm Hg) $\pm$ SEM				
	Twice daily 9 AM	Difference twice daily to once daily (9 AM)	Once daily		Difference once daily 9 AM-11 AM
			9 AM	11 AM	
Sitting-systolic	130 $\pm$ 2.3	$p < 0.02$	137 $\pm$ 3.4	129 $\pm$ 4.2	$p < 0.05$
diastolic	86 $\pm$ 1.8	NS	87 $\pm$ 2.1	84 $\pm$ 3.1	NS
Standing-systolic	131 $\pm$ 2.4	NS	134 $\pm$ 2.0	126 $\pm$ 2.3	$p < 0.05$
diastolic	88 $\pm$ 1.5	NS	89 $\pm$ 1.9	84 $\pm$ 2.1	$p < 0.05$
Supine-systolic	133 $\pm$ 3.2	NS	137 $\pm$ 3.3	130 $\pm$ 3.4	$p < 0.05$
diastolic	87 $\pm$ 0.9	NS	87 $\pm$ 2.0	84 $\pm$ 1.1	NS
Heart rate	70 $\pm$ 3	NS	73 $\pm$ 3	67 $\pm$ 2.4	$p < 0.05$

dosing at 11 AM and once daily dosing at 9 AM were not significant with the exception of the sitting systolic pressure which was significant ( $p < 0.05$ ). This was due primarily to one patient whose mean systolic pressure increased from 132 to 148 mm Hg. While the mean heart rate increased on the once daily regimen the difference was not significant. As expected all blood pressures and heart rates decreased 2 hours after the once daily dose was given (Table 1). While the decrease was statistically significant in most cases no patient had to withdraw from the study due to bradycardia (HR  $<$  50 beats/minute) or a hypotensive episode (decrease in diastolic blood pressure  $>$  20 mm Hg) and no reduction in dose was necessary. Every patient was specifically questioned at each visit for known adverse effects to propranolol. Subjectively there were no more adverse effects associated with once daily dosing than with twice daily dosing.

The results of this preliminary study indicate that single daily dosing of propranolol in hypertension is efficacious. In addition this method of dosing appears to be safe. Results of other similar studies of propranolol are consistent with the findings of this investigation. Although more study with larger patient populations is certainly recommended in the United States before widespread use of this dosing regimen, some countries have already officially approved beta blockers for administration in single daily doses for the treatment of hypertension.

The explanation that probably contributes most to the prolonged antihypertensive action of propranolol has been described by Nies and Shand. As the single oral dose is increased above about 30 mg, the hepatic extraction process becomes saturated and remains saturated throughout the usual six hour dosing interval so that drug concentrations in the blood accumulate during chronic oral administration.

With recent research in the area of simplified regimens for beta blockers and other antihypertensive agents such as methyldopa and hydralazine the prospect for exclusive twice a day and single daily dosing of all antihypertensive agents appears quite good.

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#### Regression equations and normal values for children

##### To the Editor

The report of Lewis and associates on left ventricular function in  $\beta$  thalassemia is another example of the usefulness of the combined noninvasive techniques of systolic time intervals and echocardiography in investigating the effects of various disease states on left ventricular performance. In reporting their results however the authors presented the

deviations from normal of the various measurements without regard to the fact that normal values for children differ considerably from adults in many of these parameters.

It has been known for some time that the relationship between systolic time intervals and heart rate in children is not identical to that in adults. It is not therefore valid to apply the regression equations of Wersler to children as the authors did. We have recently published regression equations which can be used as normal standards for children and which show that for a given heart rate the normal value for QS/LAET and PEP can be quite different in children than in adults. Even the ratio of PEP/LAET which is essentially independent of heart rate has a different normal value in children ( $0.30 \pm 0.04$ ) than in adults ( $0.35 \pm 0.04$ ). Similarly the normal values for adults for the chamber dimensions measured echocardiographically are not valid for children. The normal chamber dimensions *per square meter of body surface area* are larger for children who have smaller body surface areas, than for adults. Thus for example the upper limit of normal for left ventricular diastolic diameter for patient No. 19 who had a body surface area of  $0.70 \text{ M}^2$  is  $4.6 \text{ cm/M}^2$  as opposed to  $3.2 \text{ cm/M}^2$  for adults.

Approximately half of the 23 patients studied by the authors were children and in their Group 3 the majority were children. It is not valid therefore to express the measurements in the entire series in terms of deviations from the normal values of adults. For the same reason comparison of the three groups in respect to the mean values of the measurements as is shown by the authors in Figs. 2, 3, and 5

and in Table III is not valid. In order to compare the measurements in the three groups in such a mixed series, the percentage of deviation from normal should be calculated for each measurement based on the expected normal values for each individual. It would be worthwhile for the authors to recalculate their data in this fashion in order to determine if there is really a significant difference as they reported between the groups in respect to some of the echocardiographic parameters. More important it should be determined if there is not after all some degree of diminished left ventricular performance by systolic time intervals in Group 3.

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**Clinical Hypertension**, second edition. By Norman M Kaplan. M.D. Baltimore 1978. The Williams & Wilkins Company. 400 pages. Price \$41.00.

This book is intended for clinicians. This is an excellent publication on a disease which is extremely common and important. It must be treated in some manner by practically all practicing doctors. Kaplan discusses clearly diagnosis and management. The book is well written. The dietary recommendations are presented including tables listing foods for the management of hypokalemia, a constant problem when diuretic drugs are used. The index is well organized and usable and the bibliographies though brief document statements in the text effectively. The common types of hypertension are clearly defined and discussed including renovascular hypertension, aldosteronism, low renin hypertension and pheochromocytoma. This is a good book that should interest all doctors.

**Cardiac Glycosides**. Edited by G. Bodem and H. J. Dengler. New York 1978. Springer Verlag. 428 pages. Price \$79.00.

This publication includes the discussions at an international symposium held in Bonn during January 1977 on the cardiac glycosides. This series of papers summarizes very well the chemistry, pharmacology and clinical use of the cardiac glycosides. The metabolism and excretion of the various glycosides are discussed including the pharmacokinetics in renal disease and uremia. The aspects of background knowledge concerning the cardiac glycosides are important but the clinical use of the glycosides was neglected in the symposium so that the practicing physician will find little use for this publication. In fact this reviewer finds conflicts of methods for digitalizing patients. The use of the digoxin blood level is relied upon by some of the participants for judging the clinical state of digitalization of patients whereas others do not. This is also true in the hospitals and clinics throughout the world. This publication is a good reference book. The contributors do advise the reader how to digitalize a patient satisfactorily without intoxicating him even though this can be done.

**Cardiac Pathology**. By Colin M. Bloor. Philadelphia 1978. J. B. Lippincott Company. 420 pages. Price \$39.00.

This is a very good book on cardiac pathology. It is brief, succinct and thorough. The practice of good cardiology without a knowledge of cardiac pathology is impossible. Bloor's book includes discussions of the important selected problems in clinical cardiac pathology. Embryology, anatomy, physiology, and clinical manifestations are interwoven in the discussion of the pathology of congenital and acquired types of heart disease. This book is written for clinicians as well as for pathologists. The illustrations are good, the bibliography appended to each chapter is well selected, and the publication is well done. This is a good book.

**Clinical Echocardiography**. By Jacob I. Haft, M.D. and Michael S. Horowitz, M.D. Mount Kisco, New York, 1978. Futura Publishing Company, Inc. 248 pages. Price \$19.00.

Many books are appearing on the subject of echocardiography. This book is another one which really adds very little new to the field. Those interested in the subject will find this book can supplement others very little. The discussion of the interventricular septum is interesting. This is one structure in which the function is observed best by echocardiography. This is a satisfactory book on echocardiography.

**Clinical Echocardiography**. By Navin C. Nanda and Raymond Gramiak. St. Louis 1978. The C.V. Mosby Company. 401 pages. Price \$37.00.

This is an excellent book on echocardiography. The authors have contributed considerably to the development of echocardiography as a clinical diagnostic tool. The presentations are authoritative and reflect a great deal of personal experience and thought. The book is divided into two parts: (1) fundamentals of echocardiography and (2) clinical echocardiography. The latter consists of chapters concerned with each anatomic structure of the heart, such as the four valves, the left ventricle, prosthetic valves, pericardial fluid and two-dimensional echocardiography. The text is clear and the illustrations are good but do not reveal the problems of obtaining excellent recordings. The diagrams are extremely helpful in clarifying the two-dimensional recordings by sector scan. This is an excellent and authoritative book on echocardiography.

**Clinical Echocardiography**. Edited by Morris N. Kotler and Bernard L. Segal. Philadelphia 1978. F.A. Davis Company. 371 pages. Price \$35.00.

This is another excellent issue of *Cardiovascular Clinics*. The subject is timely and deals with a rapidly developing field. The many contributors have reviewed the field very well, including a discussion of training physicians and technicians. The sector scan is reviewed as well as many important clinical applications of echocardiography. This volume should not only interest trainees in cardiology and internal medicine but physicians in general who will be using echocardiography more and more. This procedure is an important new development in medicine. Unfortunately, some observers overread the tracings and attempt to quantitate hemodynamic phenomena while the method has not yet made accurate quantitation of most hemodynamic and cardiodynamic phenomena possible. The critical reader will learn this for himself from the various discussions. Many of the indices described need to be evaluated by reliable quantitative studies and even such reliable standards are not yet available. This volume is a good addition to the echocardiographic literature.

## Books received

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**Regulation of Ventilation and Gas Exchange** Edited by Donald G. Davies and Charles U. Barnes, New York, 1978, Academic Press, Inc. 308 pages, Price \$22.00

**Preventing Coronary Heart Disease** By A. C. Artz, E. M. Epstein, K. H. Gunther, M. Kornitzer, J. Menard, T. Strasser

and R. C. DeBoeck, Assen, The Netherlands, 1978, Van Gorcum & Company B.V., 66 pages

**Stades Surgical Diseases of the Chest** Edited by Donald Brian Effler, St. Louis, 1978, The C. V. Mosby Company, 839 pages, Price \$59.50



## Basic Cardiology for the Practicing Physician

A course entitled Basic Cardiology for the Practicing Physician will be held at the Ahwahnee in Yosemite National Park, California, on March 16 through 19, 1980. This course is sponsored by the Department of Medicine, Division of Cardiology and Extended Programs in Medical Education, University of California School of Medicine, San Francisco. This course is designed for physicians in the fields of Family Practice, General Practice, and Internal Medicine to update their knowledge of current cardiology diagnostic methods through lectures and workshops with case studies. The course is approved for 15 hours of Category 1 Credit. For further information, please contact: Extended Programs in Medical Education, Room 601, University of California, Third and Parnassus Aves., San Francisco, Calif. 94143. Telephone: (415) 666-4251.

## Computers in Critical Care Medicine

The second international symposium on Computers in Critical Care and Pulmonary Medicine will take place in Lund, Sweden, from June 3 through 8, 1980. Correspondence regarding abstracts, papers, registration, and symposium accommodations should be addressed to: Mrs. Bodil Richardson, Symposium Secretary, Kliniskt Fysiologiska Avdelningen (Department of Clinical Physiology), Laxarett 9, S-221 83 Lund, Sweden.

## Clinical Approach to Exercise Testing

A seminar entitled Clinical Approach to Exercise Testing will be held on April 10 through 12, 1980, at the Sheraton Sand Key Hotel, Clearwater Beach, Fla. Program directors are Stephen I. Chesser, MD, and Pamela I. Clark, RN. For further details, contact: Ms. Billie N. Chiles, Tampa Tracings, P.O. Box 1245, Tarpon Springs, Fla. 33489.

## Workshop in Echocardiography

A Workshop in Echocardiography will be presented on March 27 through 30, 1980, at the Don Cesar Beach Resort Hotel, St. Petersburg Beach, Fla. The workshop will be directed by Louis F. Teichholz, MD, of the Mount Sinai School of Medicine, New York City. For further information regarding this workshop, contact: Ms. Billie N. Chiles, Tampa Tracings, P.O. Box 1245, Tarpon Springs, Fla. 33489.

## Tenth Heart Congress

On September 23 through 28, 1980, the Tenth Heart Congress of the International Society for Heart Research will be held in Moscow, USSR. For further information, contact: Professor V. N. Smirnov, National Cardiology Research Center, Academy of Medical Sciences, Pirogovsky Lane 10, Moscow 101687, USSR.

## Editorial

### The complications of coronary arteriography a problem that won't go away

Steven A Schroeder M D

San Francisco Calif

Coronary arteriography may be the fastest growing major invasive procedure of the past decade. For example, at the Montreal Heart Institute the frequency of coronary arteriography increased from about 71 procedures per year in 1965 and 1966 to about 1 000 cases per year by 1970. In 1975 cardiac catheterization (predominantly coronary arteriography) was the most common surgical procedure reported at the University of California San Francisco hospitals, occurring almost twice as frequently as the next most common procedure (cesarean section).

The value of this procedure undoubtedly derives from its establishment as the gold standard for the presence of coronary artery disease. This, combined with considerable professional disagreement concerning its indications as well as its relative ease of performance and widespread availability in the community, contributes to its popularity. Possible reasons for this last factor include the large number of cardiologists being trained (in 1975 1 052 cardiology certificates were awarded by the American Board of Internal Medicine, accounting for 19 per cent of all certificates awarded by the Board), the increasingly aggressive approach to coronary artery disease and financial incentives for the performance of surgical rather than medical care.

Along with the obvious and well-touted benefits of coronary arteriography, however, are a set of associated risks. Since these have been summarized in several excellent reviews,<sup>1-4</sup> a detailed summary will not be attempted here, except to emphasize two points. First, substantial variability exists in mortality and morbidity rates among different catheterization laboratories; for example, published mortality rates range from as low as 0.1 per cent to one extraordinary case of an institution with a reported rate of 8 per cent. Second, rates of catheter-associated deaths and severe complications do not appear to be decreasing. Factors associated with increased risks of mortality and morbidity include use of the femoral as opposed to the brachial artery approach, inexperience of the operator and/or the laboratory, low volume of cases performed at the laboratory, presence of associated diseases, especially significant stenosis of the left main coronary artery, long and complex procedures, and absence of systemic heparin given to prevent thromboembolic complications. In reviewing these data, Judkins and Gander suggest that laboratories with death rates in excess of 0.3 per cent should stop doing procedures altogether and reassess program goals and commitments.

It was because of concern about the risks of invasive diagnostic procedures that Drs Keith Marton, Brian Strom, and I recently undertook a small pilot study of their frequency and complication rates on all patients of the medical services of two university hospitals. The results, published in the December 1978 *Archives of Internal Medicine*,

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*cine* showed that in the period studied invasive procedures were commonly performed 47 per cent of the 303 patients admitted to the two services underwent at least one invasive procedure and each of these had an average of 1.6 such procedures. The most frequent procedure was catheterization of the left side of the heart occurring in 34 patients. Nineteen of these procedures were coronary arteriograms and most also included right sided catheterization. Lumbar puncture was the second most common procedure occurring in 31 patients. Catheterization limited to the right side of the heart ranked sixth with 12 cases. Altogether cardiac catheterization accounted for 20 per cent of all invasive procedures performed in the study.

Twenty nine complications of procedures were recorded in 20 patients. The largest number of complications resulted from left sided catheterization totalling ten incidents in six patients. Fortunately these were relatively minor including hemorrhage (three patients), fever (two patients) and arrhythmia, hypotension, phlebitis, pulmonary edema and psychological trauma (one case each). The complication of psychological trauma refers to a patient who deferred needed valvular surgery because of anxiety generated by treatment of post catheterization hypotension. Although no deaths were recorded three of the complications required specific therapy such as blood transfusion and six required therapy as well as prolonged hospitalization. During the time period studied a patient undergoing left sided cardiac catheterization had a 16 per cent chance of having a complication that required therapy and/or prolonged hospitalization. None of the severe complications that can result from the procedure such as systemic emboli, loss of limb, myocardial infarction or perforation occurred.

While the frequency of minor nonfatal complications in our small study is higher than in the published literature we believe that the published incidence of complications may be misleadingly low. To begin with institutions with high complication rates do not usually report their experience thereby making generalizations from the published literature unreliable. Reports that are published contain at least three important biases. The first is that multi-institutional surveys may under represent hospitals with more frequent complications. For example the survey

of 313 coronary arteriography laboratories by Adams, Fraser and Abrams only received results from 46 per cent of the institutions contacted. The second bias is that routine reporting underestimates complication rates. For example careful studies of hospital infections show actual infection rates that are two or three times greater than those routinely reported.<sup>11</sup> The third bias derives from the short observation period during which complications are sought thus excluding late complications such as post transfusion hepatitis.

Five years ago Judkins and Cander concluded that the high reported rates of complications of coronary arteriography are unacceptable.<sup>12</sup> There are at least four different strategies that could help make these risks more acceptable. First there should be routine and accurate surveillance of complication rates including mortality at all laboratories performing coronary arteriography. These data should be analyzed periodically and should be readily available to all physicians and patients. (If the laboratory can provide stratified risks according to clinical conditions such as age or presence of left main disease the data will be that much more meaningful. It should be remembered however that the lowest complication rates are likely to occur in perfectly healthy patients.) Each laboratory should determine ahead of time the level at which complication rates are unacceptable and be prepared to consider a set of corrective actions including closing the laboratory. This individual laboratory surveillance effort must also be supplemented by coordinated national programs. Surveys such as the one by Adams, Fraser and Abrams should be repeated periodically, hopefully with a greater than 46 per cent participation rate. Better still would be a system of periodic national surveillance conducted by a national agency such as the Center for Disease Control in Atlanta, Georgia. Such a model already exists for nosocomial infection surveillance.

Second if periodic surveys continue to show some laboratories with unacceptably high fatality and complication rates (adjusted for disease severity and age) strategies either to improve or close down those laboratories should be available. For example malpractice premiums could be adjusted to reflect actual complication rates. There could be enforcement of minimal resources for catheter laboratories along the lines of the Report of the Inter Society Commission for

Heart Disease Resources and performance criteria of catheterization laboratories could be included as part of hospital accreditation procedures.

Third attempts should be continued to achieve a professional consensus regarding indications for the procedure. The Report of the Ad Hoc Committee on the Indications for Coronary Arteriography is one such attempt.<sup>1</sup> However subsequent reviews of coronary arteriography have continued to present extremely broad indications for the procedure including for example the need to know as an indication considered apart from the likelihood of subsequent operative intervention.<sup>1</sup>

Fourth the risks of coronary arteriography need to be emphasized more in the current medical literature. In Hurst's recent 2 000 page text on heart disease<sup>2</sup> only one half page is devoted to complications of coronary arteriography and no risk figures are provided. Grossman's standard text on *Cardiac Catheterization and Angiography* mentions the major complications of coronary arteriography but concludes that fortunately the incidence is low.

Given that most physicians are reluctant to prescribe drugs such as chloramphenicol that carry a risk of fatal reaction of approximately one in 40 000 it is hard to agree that fatality rates ranging from one per thousand to 80 per thousand are low. Coronary arteriography is clearly one of the reasons that cardiology has entered into a golden age during the past two decades.<sup>1</sup> Nevertheless there must be greater awareness of the procedure as associated risks and wider knowledge of the extent of those risks at each institution. Availability of such data will at the very least enhance clinical decision making clarify benefit risk issues and offer legal protection. It might even lead to a decrease in the rate of complications of coronary arteriography.

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# Frequency and direction of interatrial shunting in valvular pulmonic stenosis with intact ventricular septum and without left ventricular inflow or outflow obstruction

An analysis of 127 patients treated by valvulotomy

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It is well recognized that patients with valvular pulmonic stenosis with intact ventricular septum often have shunts at the atrial level. Although right to left shunting at the atrial level in these patients has received considerable attention, relatively little attention has been directed toward the patients with pulmonic stenosis with left to right interatrial shunts. In this report the frequency and direction of atrial shunting is described in 127 patients who underwent pulmonic valvulotomy unassociated with ventricular septal defect. Characteristics of the patients with left to right interatrial shunts are compared to those of the patients with right to left interatrial shunts and the mechanism of the shunting is discussed.

## Patients studied and findings

The records of patients undergoing operation in the National Heart Institute from 1955 through 1977 were reviewed. A total of 127 patients with valvular pulmonic stenosis with intact ventricular septum and without obstruction to left ventricular inflow or outflow or with associated aortopulmonary arterial communication under-

went operative relief of the valvular obstruction during this period. Of the 127 patients 93 (73%) had no shunt at the atrial level detected preoperatively at cardiac catheterization by indicator dilution curves and no defect in the atrial septum was found in them at operation. Each of the remaining 34 patients (27%) had a defect in the atrial septum found at operation and a shunt at the atrial level had been detected preoperatively by dye dilution curves (with injection of cardiogreen into the inferior vena cava and into the main pulmonary artery) in 30 (88%) of them. Statistical methods used were Student's *t* test of significance for differences between two groups (patients with right to left shunts vs those with left to right shunts) or paired data (comparison of two pressure measurements within individual patients in a group). Data are expressed as mean  $\pm$  standard error of mean.

These 30 patients were divided into two major groups determined by the direction of the shunt at the atrial level: 19 patients with right to left shunts (four of them [patients BB, LP, TR, and CC, Table I] also had minute left to right shunts by pulmonary arterial dye curves) and 11 patients with left to right shunts and no evidence of right to left shunting. Clinical hemodynamic and operative observations in each of the 30 patients is detailed in Table I.

The 19 patients with right to left shunts compared to the 11 patients with left to right shunts tended to be older (average age 18 vs 14 years)

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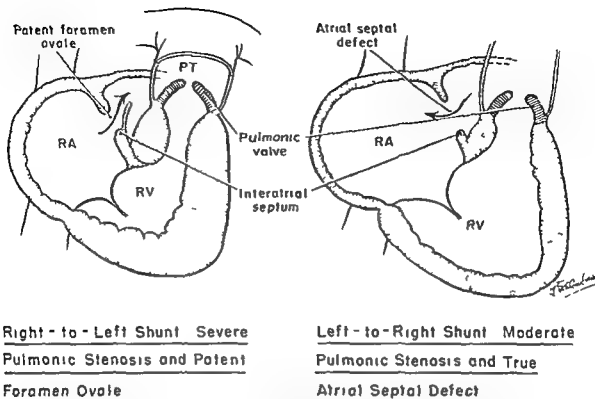


Fig 1 Diagram displaying the essential differences between patients with pulmonic stenosis and right to left interatrial shunts and those with left to right interatrial shunts. The former produces primarily a pressure overload right ventricular type heart and the latter a volume overload right ventricular type heart.

and had higher average blood hematocrit levels (51 vs 42) but neither of these were statistically significant. The systemic arterial oxygen saturation was less in the patients with right to left shunting ( $85 \pm 2$  vs  $93 \pm 1$   $p < 0.05$ ). The patients with right to left shunting had lower systolic pulmonary arterial pressures ( $13 \pm 1$  vs  $20 \pm 1$  mm Hg  $p < 0.001$ ) but diastolic pressures were similar ( $6 \pm 5$  vs  $9 \pm 1$  mm Hg NS). Right ventricular systolic pressures were greater in the patients with right to left shunts ( $136 \pm 10$  vs  $80 \pm 5$  mm Hg  $p < 0.001$ ) but right ventricular diastolic pressures were similar ( $7$  vs  $8$  mm Hg NS). The peak systolic pressure gradients between right ventricle and pulmonary trunk were greater in the group with right to left shunts ( $120 \pm 11$  vs  $60 \pm 5$   $p < 0.001$ ). Right atrial a ( $9 \pm 1$  vs  $8 \pm 1$  mm Hg NS) and v waves ( $5 \pm 0.5$  vs  $5 \pm 1$  mm Hg NS) were similar in the two groups but mean right atrial pressures were less in the group with right to left shunts ( $4 \pm 1$  vs  $5 \pm 0.5$  mm Hg  $p < 0.01$ ). The defects in the atrial septum were much smaller (average  $1.1 \pm 0.1$  cm in diameter) in the 19 patients with

right to left shunts than in the 11 patients with left to right shunts (average  $2.8 \pm 0.1$  cm in diameter). This difference in size of the interatrial defect in the two groups of patients is further emphasized by the method chosen to close the defect at operation in 16 (84%) of the 19 patients with right to left shunts and in only two (18%) of the 11 patients with left to right shunts. The defect in the atrial septum was closed by suture alone indicating that the defect in these 18 patients (60% of the total of 30 patients valvular pulmonic stenosis and atrial shunts) was small and simply a patent foramen ovale. In contrast in only three (16%) of the 19 patients with right to left shunts and in nine (82%) of the 11 patients with left to right shunts the defect in the atrial septum was closed by patch indicating that these defects were large and therefore not a simple patent foramen ovale but a true atrial septal defect or at least a severely stretched membrane of the fossa ovalis.

As shown in Table I comparison of the right and left atrial pressures in the patients with right to left shunts showed little to no di

Table 1 Observations in each of 30 patients with valvular pulmonic stenosis and interatrial shunts

Pt	Age (yrs)	Sex	SA Het (°)	SA O Sat (%)	Pressure in mm Hg												
					PV		RV		RV PA	RA			LA				
					s	d	s	d	avg	a	c	m	a	c	m		
Right to left shunt																	
RR	3	M	47	80	10	6	100	8	90	10	6	5	8	11	5	5	
CI	4	F	41	80	10	5	110	5	100	10	4	5	10	3	4	4	
EP	4	F	48	88	—	—	175	10	—	—	—	—	8	4	5	5	
MC	5	F	41	87	—	4	80	4	78	4	0	2	4	0	2	2	
AM	6	F	42	91	—	—	120	7	—	8	5	4	8	11	5	5	
DJ	6	F	42	93	10	7	107	3	97	4	4	2	—	9	3	3	
JW	7	M	51	80	12	6	100	5	89	—	—	4	—	—	—	—	
CC	11	F	60	87	18	5	118	5	100	4	7	4	11	—	4	4	
BB	11	F	42	91	—	—	130	5	—	—	—	5	—	—	—	—	
DP	13	M	49	84	24	12	100	17	177	10	10	6	—	—	—	8	
TR	15	F	49	91	18	9	210	10	222	9	6	5	9	—	3	3	
LI	20	F	60	68	12	4	192	8	180	10	11	5	—	—	—	—	
CL	24	F	54	—	—	—	168	6	—	11	4	2	9	3	7	7	
FS	27	F	7	82	10	10	16	0	100	9	1	4	8	0	4	4	
SR	28	F	61	77	9	5	143	5	134	8	6	2	9	5	5	5	
RW	34	M	44	91	10	4	70	4	55	11	11	4	—	—	—	—	
SM	37	M	47	93	12	6	78	6	67	9	7	4	11	—	6	6	
VD	40	F	62	87	12	6	102	10	140	9	3	4	—	—	—	—	
AN	43	F	70	84	12	8	182	17	170	12	3	4	—	—	—	—	
Totals 18 ± 3					51 ± 2	8 ± 2	11 ± 1	6 ± 0.5	130 ± 10	7 ± 1	170 ± 11	9 ± 1	5 ± 0.5	4 ± 0.5	8 ± 0.5	5 ± 1	4 ± 0.5
Left to right shunt																	
ST	4	F	43	93	28	8	115	17	8	17	8	8	17	10	8	8	
JS	6	M	44	92	18	8	—	11	57	5	4	3	—	—	—	—	
L7	6	F	30	88	24	14	68	10	47	4	0	2	8	3	5	5	
RL	8	F	41	94	24	12	70	10	44	9	—	5	11	9	8	8	
JH	11	F	41	91	15	8	70	0	5	—	2	5	12	11	4	4	
JK	13	M	42	93	10	5	60	5	4	10	3	6	11	1	2	2	
RS	1	M	46	94	20	8	80	8	07	11	—	5	14	12	6	6	
WP	13	M	43	87	12	3	78	6	67	—	—	7	—	—	6	6	
RR	19	F	71	92	22	16	110	13	88	10	7	8	16	14	10	10	
RR	27	F	42	9	22	8	60	10	43	10	9	8	—	—	8	8	
CC	28	F	41	93	18	6	82	4	64	11	4	2	5	5	4	4	
Total 14 ± 3					47 ± 1	20 ± 1	9 ± 1	80 ± 5	8 ± 1	60 ± 5	8 ± 1	5 ± 1	5 ± 0.5	11 ± 1	7 ± 1	7 ± 0.5	7 ± 0.5
NS					NS		NS		NS		NS		NS		NS		NS

Abbreviation: a = aortic, ASD = atrial septal defect, d = end-diastolic, Het = hematocrit, m = mean, p = patch, PA = pulmonary artery, p = pressure, q = pulmonary, q/s = pulmonary flow ratio, RA = right atrium, RV = right ventricle, s = systolic, t = trans, u = uterine, v = ventricular, w = wall, x = x-ray, y = year, z = zone, A = anterior, B = posterior, C = central, D = distal, E = external, F = internal, G = superior, H = inferior, I = lateral, J = medial, K = proximal, L = distal, M = middle, N = normal, O = obstructed, P = patent, Q = closed, R = regular, S = irregular, T = thin, U = thick, V = valvular, W = without, X = with, Y = yes, Z = no.

despite a small defect in the atrial septum. In contrast with the exception of one patient in those with left to right interatrial shunts the left atrial pressures were higher than the right atrial pressures despite the presence of a relatively large defect in the atrial septum. Among the eight patients with left to right interatrial shunts in whom the a and m pressures were recorded from both atria the right atrial and their corresponding average left atrial pressures were as follows:  $a = 8 \pm 1$  and  $11 \pm 1$  mm Hg ( $p < 0.01$ );  $v = 5 \pm 1$  and  $7 \pm 1$  mm Hg (NS) and

mean =  $5 \pm 0.5$  and  $7 \pm 0.5$  mm Hg ( $p < 0.01$ ). Among the 11 patients with right to left interatrial shunts these corresponding average pressures were as follows:  $a = 9 \pm 1$  and  $8 \pm 0.5$  mm Hg (NS);  $v = 5 \pm 0.5$  and  $5 \pm 1$  mm Hg (NS) and mean =  $4 \pm 0.5$  and  $4 \pm 0.5$  mm Hg (NS).

The right ventricular end diastolic pressures tended to be lower than the left ventricular end diastolic pressures in the patients with right to left interatrial shunts but this difference was not statistically significant. In the patients with exclusive left to right shunts left ventricular

<i>LV</i>		$\frac{qf}{qS}$	<i>Sz c</i> ( <i>cm</i> ) <i>ASD</i>	<i>Closure</i> ~1 <i>SD</i> <i>bv</i>
<i>s</i>	<i>d</i>			
—	—	—	10	Su
100	5	—	1.5	Su
—	—	—	10	Su
100	5	—	10	Su
—	—	—	0.8	Su
107	9	—	10	Su
100	—	—	2.2	I
100	4	—	15	Su
140	—	—	10	Su
—	—	—	15	P
96	6	—	10	Su
—	—	—	10	Su
—	—	—	10	P
100	0	—	10	Su
117	—	—	1.5	Su
—	—	—	10	Su
—	—	—	10	Su
—	—	—	10	Su
—	—	—	07	Su
110 ± 5	6 ± 1		11 ± 0.1	
129	13	11	20	P
—	—	14	—	P
115	10	—	50	I
—	—	13	1.5	Su
127	0	1.8	25	P
100	2	—	2.5	P
127	12	14	30	P
138	6	16	30	P
130	—	15	1.5	Su
—	—	1.8	30	P
80	6	13	40	P
101 ± 6	6 ± 1		28 ± 0.1	
NS	NS			

end diastolic pressures tended to be lower but not significantly different. Of the nine patients with right to left shunts in whom both right and left ventricular end diastolic pressures were recorded the right averaged  $7 \pm 1$  and the left  $6 \pm 1$  mm Hg (NS). Of the eight patients with exclusive left to right shunts in whom both right and left ventricular end diastolic pressures were recorded the right averaged  $8 \pm 1$  and the left  $6 \pm 1$  mm Hg (NS).

In addition to searching the operative records for patients with valvular pulmonic stenosis with

intact ventricular septum the records of patients with closure of atrial septal defect without ventricular septal defect also were examined. A total of 436 patients underwent operative closure of atrial septal defect (excluding ostium primum type) at the National Heart Institute from 1955 through 1977. Of this number 31 (7%) (included above) had valvular pulmonic stenosis with normally functioning left sided cardiac valves and all underwent valvulotomy.

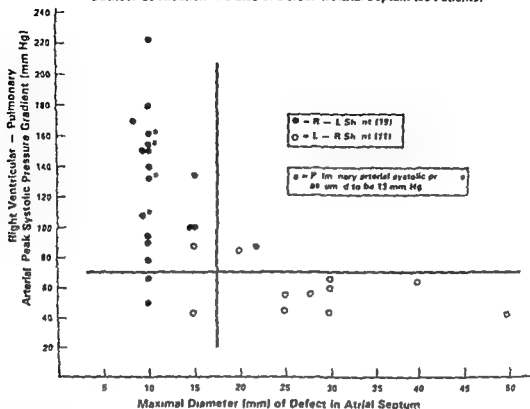
### Comments

The above observations in patients with congenital valvular pulmonic stenosis without ventricular septal defect or left ventricular inflow or outflow obstruction indicate that shunting at the atrial level is fairly common and that the shunting is more commonly right to left than left to right. Among our 127 patients with isolated pulmonic stenosis 30 (24%) had shunts detected preoperatively by indicator dilution curves at the atrial level. In 19 (63%) the shunt was exclusively or nearly so right to left (hereafter called right to left) and in the other 11 (37%) the shunt was entirely left to right (hereafter called left to right). In all 19 patients with right to left shunts detected at cardiac catheterization a defect at the atrial level had been suspected clinically because of central cyanosis either at rest or with exertion or both. Of the 11 patients with left to right shunts no shunting at this level was suspected before cardiac catheterization in 4 and an atrial septal defect was suspected in 7. In 10 of the latter 11 patients pulmonic valve stenosis was diagnosed clinically before cardiac catheterization and in the remaining one patient atrial septal defect was the only pre catheterization diagnosis. All 11 patients were acyanotic even with strenuous exertion. Whereas none of the 19 patients with right to left shunts had wide splitting of the second heart sound at the cardiac base by auscultation (most had single second heart sounds in this area) six of the 11 with left to right shunts had wide if not fixed splitting of the second heart sound by either auscultation or phonocardiography or both.

The explanation for the differing direction of the shunting at the atrial level in the 30 patients appears to be the size of the defect in the atrial septum and the degree of obstruction to right ventricular outflow. With one exception the defect in the atrial septum was small (average = 1.1 cm) in each of the 19 patients with



**PULMONIC VALVE STENOSIS AND INTERATRIAL SHUNTING**  
**Relation Between Degree of Right Ventricular**  
**Outflow Obstruction and Size of Defect in Atrial Septum (30 Patients)**



**Fig 2** Relation between the degree of the right ventricular outflow obstruction and the size of the defect in the atrial septum as shown

right to left shunts and as determined from descriptions of the atrial septum at operation was simply a patent foramen ovale. Because the membrane of the fossa ovale is located on the left side of the atrial septum, higher pressures on the right than on the left side of the atrial septum appear to be responsible for the shunts being right to left in the presence of a simple patent foramen ovale. If the foramen ovale is patent but valvular competent, exclusive left to right shunting at the atrial level is impossible even if the left atrial pressures are considerably higher than the right atrial pressures because the membrane in this circumstance simply will be pressed against the septum not away from it. Among the 19 patients with right to left shunting, at the atrial level, however, no significant differences in the pressures (A wave, V wave, and mean) in the right atrium compared to their respective counterparts in the left atrium were observed (Table I). The usual explanation for right to left shunts occurring in the presence of right ventricular pressure overload is a decrease in right ventricular compliance. Of course, no measurement of ventricular

compliance was made, but neither right atrial nor right ventricular end diastolic pressure was greater than their corresponding pressure on the left side.

The explanation for the left to right shunts at the atrial level in the other 11 patients appears to reside at least in part in the relatively large size (avg 2.8 cm in diameter) of the defect in the atrial septum. Of these 11 patients, the defect in the atrial septum was closed by a patch in nine, whereas a patch was utilized for closure in only three of the 19 patients with right to left shunts. Among the eight recorded, the left atrial pressures, including A and V waves and mean pressures, were higher in the left atrium than their respective counterparts in the right atrium. Although in five of the eight patients recorded, the left ventricular end diastolic pressure was equal to or higher than the right ventricular end diastolic pressure, the average left ventricular end diastolic pressure was lower than the average right ventricular end diastolic pressure (6.0 vs 7.2 mm Hg).

Another major hemodynamic difference be-

tween the patients with right to left shunts and those with left to right shunts at the atrial level was the magnitude of the obstruction to right ventricular outflow. The 19 patients with right to left shunts had right ventricular to pulmonary arterial peak systolic pressure gradients twice as high as did the 11 patients with left to right shunts ( $120 \pm 60$  mm Hg). Accordingly the right ventricular systolic pressures were nearly twice as high in the patients with right to left shunts compared to those with left to right shunts ( $136 \pm 80$  mm Hg) but the right ventricular end diastolic pressures in the two groups were similar (8 and 7 mm Hg respectively).

Although numerous reports<sup>1-7</sup> have emphasized the frequency of right to left shunting at the atrial level in patients with isolated pulmonic stenosis, relatively few have focused on patients with exclusive left to right shunting at the atrial level. The first to do so appears to have been Abrahams and Wood in 1951. These authors described clinical observations in 52 patients with isolated pulmonic stenosis, 37 of whom had intact atrial septa and 15 of whom had defects in the atrial septum. In eight of the latter 15 patients the shunt at the atrial level was right to left and all of them had evidence of severe pulmonic valve obstruction. The other seven had evidence of left to right shunting at the atrial level and all had only mild pulmonic stenosis. Abrahams and Wood reasoned that the patient with a venoarterial interatrial shunt had a patent foramen ovale and that the patient with an arteriovenous interatrial shunt had a true atrial septal defect. Anatomic confirmation of this reasoning however was not available. Deugher and Zak described predominant left to right shunting at the atrial level in one of their four patients with isolated pulmonic stenosis. Broadbent and associates observed five patients with isolated pulmonic stenosis and left to right shunting at the atrial level and pointed out that the right ventricular outflow obstruction was mild in four (peak systolic pressure gradients from 22 to 35 mm Hg) and severe in only one (peak systolic pressure gradient = 122 mm Hg). Again none of their five patients had undergone cardiac operation or necropsy. Moffitt and associates described two patients with isolated pulmonic stenosis and left to right interatrial shunting; the degree of right ventricular outflow obstruction in each was mild (gradients 25 and 29 mm Hg respectively). Few subsequent reports have

emphasized or discussed mechanisms of left to right shunting at the atrial level in patients with isolated pulmonic stenosis.

In conclusion patients with isolated pulmonic stenosis and right to left interatrial shunts usually have small defects in the atrial septum (patent foramen ovale) and severe pulmonic stenosis. Patients with isolated pulmonic stenosis and left to right interatrial shunts usually have relatively large defects in the atrial septum (true atrial septal defect) and mild to moderate obstruction to right ventricular outflow.

### Summary

This report summarizes observations in 127 patients who underwent pulmonic valvulotomy for valvular pulmonic stenosis with intact ventricular septum and without obstruction to left ventricular inflow or outflow. Of the 127 patients 30 (24%) preoperatively by dye dilution curves had shunting at the atrial level. In 19 (63%) the shunt was right to left and in the other 11 (27%) entirely left to right. The patients with right to left interatrial shunts had severe pulmonic valve stenosis (average peak systolic pressure gradient =  $120 \pm 11$  mm Hg) and small (average diameter  $1.1 \pm 0.1$  cm) sized defects in the atrial septum (patent foramen ovale). In contrast the patients with left to right shunts had mild to moderate pulmonic valve stenosis (average peak systolic pressure gradient =  $60 \pm 5$  mm Hg) and relatively large (average diameter =  $2.8 \pm 0.1$  cm) defects in the atrial septum (true atrial septal defect). The patients with right to left interatrial shunts had no significant differences in right versus left atrial pressures. The patients with left to right interatrial shunts however had left atrial pressures significantly greater than right atrial pressures ( $7 \pm 0.5$  vs  $5 \pm 0.5$  p < 0.05). No significant differences were found in ventricular end diastolic pressures.

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# Serial myoglobin vs CPK analysis as an indicator of uncomplicated myocardial infarction size and its use in assessing early infarct extension

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An assay for the presence of myoglobin in urine or serum has been available for many years and has been used as a marker for the presence of myocardial necrosis. As has been previously noted, release of myoglobin from myocardial cells probably only occurs after irreversible cellular necrosis. However, the inability to distinguish myocardial from skeletal myoglobin limits its specificity as a clinical tool. Myoglobin does have the distinction of being one of the first biochemical markers of myocardial damage to appear in the serum and is one of the most rapidly cleared. Hence, fluctuations in serum myoglobin content should separate episodes of necrosis occurring during the course of a documented acute infarction. Indeed, Kagen and associates have shown a stepwise phenomenon of myoglobin release suggesting that a myocardial infarction is a series of separately occurring episodes of necrosis.

Unlike the other biochemical markers which are cleared through the reticuloendothelial system, myoglobin is cleared through the kidney. In addition, it has been shown that myoglobin is

metabolized by the kidneys as well, making renal function and renal blood flow very important in determining serum levels. Hence, changes in cardiac output and renal perfusion during acute infarction may affect myoglobin clearance and serum levels. We therefore chose patients with normal renal function and hemodynamically uncomplicated infarction to study the appearance and clearance characteristics of myoglobin to assess the use of myoglobin as an indicator of the size of an infarct and to determine if myoglobin can identify the progression or extension of myocardial necrosis.

## Methods

Patients were evaluated upon arrival at the emergency room and were considered for inclusion if the clinical event had occurred and a diagnostic electrocardiogram had been recorded within the previous six hours. They were excluded if renal function as determined by serum creatinine was abnormal, if other significant illness was present, or if they gave a history of a previous infarction, strenuous activity in the preceding 24 hours, recent intramuscular injections, or cardiovascular surgery. From all patients entered, those who remained in Killip Class I for the duration of their Coronary Care Unit (CCU) stay ( $n = 8$ ) formed the basis for this study.

All events were timed from the initial onset of chest pain or symptoms that brought the patients

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Table I Characteristics of myoglobin appearance and clearance following an acute myocardial infarction

Patient no	Age	Infarct location	Myoglobin						
			Peak (ng/ml)	Symptom to peak (hrs)	Symptoms to elevation (hrs)	Duration of elevation (hrs)	Serum half life (hrs)	Infarct size mvo ng hrs/mL	Infarct size CPK gm/eq
1	33	Inf post	183	0		24	10	226	114
2	57	Ant-sep	280	-	4	34	12	341	139
3	60	Inf	250	4	3	18	4	193	81
4	64	Inf	1220	9	4	34	3	761	371
5	34	Ant-sep	1290	4	4	17	4	839	443
6	33	Inf	370	10	4	24	-	573	214
7	33	Inf lat	410	6	4	24	-	298	200
8	36	Inf	208	6	3	14	6	124	6
Mean	55.3		511	7.9	3.3	23.6	7.4	406	218
SD	9.2		440	2.3	0.64	7.4	2.8	261	134

Inf = inferior; Post = posterior; Ant = anterior; Sep = septal; Lat = lateral

to the hospital. While in the CCU the patients were examined daily by one of the investigators. Note was made of time of any chest pain after admission.

Blood was sampled in the emergency room and upon arrival in the CCU and then every three hours for at least the first 30 hours (in some cases longer) and then every five hours for a total of 50 hours after CCU admission. The blood was drawn through an indwelling heparin lock and was spun, separated, and frozen for later analysis.

The serum was analyzed for CPK (total) levels using the automated analyzer modification of the Rosalki assay and acute infarct size was determined using previously described methods at Washington University in the laboratory of Dr Robert Roberts. The serum was also analyzed for its myoglobin content by radioimmunoassay using a kit from Nuclear Medical Systems Inc, Newport Beach, Calif. These samples were analyzed in duplicate. Values varied by less than 7% and the mean value was reported. The results were displayed by graph of myoglobin concentration in ng/ml vs time.

An index of infarction size was hand-calculated by measuring the area under the myoglobin concentration time plot asuming baseline to be the steady state levels of normal value once the levels returned to within normal range. Myoglobin half life was determined by analysis of the plot of logarithm of myoglobin concentration vs time.

The data were analyzed using linear regression

analysis and all values are reported as mean  $\pm$  standard deviations.

## Results

**Patient profile.** Of the eight patients eligible for this study, there were five male and three females. In all patients, infarction was confirmed by electrocardiographic evolution, enzymes (typical profile of LDH, SGOT, and presence of CPK-MB) and in the four cases where performed, positive TC-PYP myocardial scans.

Patients averaged 55.3 years in age (range 34 to 64 years). Six patients sustained inferior wall transmural MI (Q waves II, III, & aVF) and two anterior transmural MI (Q waves in Lead V<sub>1</sub>). Of the inferior MI patients, one had ECG (No 1 in Table I and Fig 3) and TC-PYP scan evidence of posterior wall involvement (R wave greater than S wave in Lead V<sub>1</sub>) and one (No 7) had involvement of the lateral wall (Q waves in Leads V<sub>4</sub>). All patients included had normal renal function documented by normal serum creatinine and a normal creatinine clearance in the first 24 hours after admission. All remained in Killip Class I throughout hospitalization. None of the patients required cardioversion or defibrillation and none had intramuscular injections. No patient had any sustained hypotension during the course of the study. All patients were discharged alive from the hospital.

During the study period (the first 50 hours after the onset of symptoms) six of eight patients

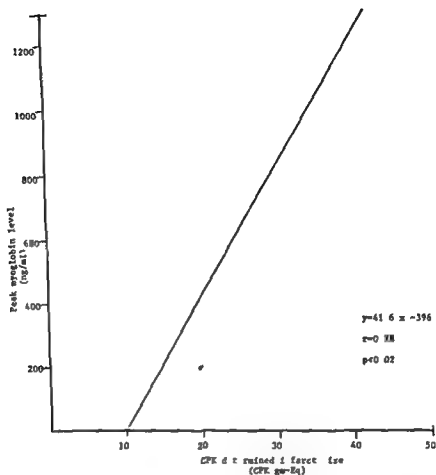


Fig 1 Correlation between peak myoglobin levels and CPK-determined infarct size

experienced two to five episodes (mean 3.5 per patient) of chest pain. Of all the episodes of chest pain, only one (patient No 1) had documentation of extension and that was posterior wall extension as noted by ECG.

#### Myoglobin appearance and clearance characteristics (Table I)

All times were considered relative to the first onset of symptoms. Normal serum myoglobin is less than 85 ng/ml. The time of appearance of myoglobin relative to patient's first symptoms was  $3.88 \pm 0.64$  hours. In the four patients whose myoglobin was already elevated at the time of first blood sample, the time from symptoms to first sample was arbitrarily considered appearance time.

The time from onset of symptoms to peak myoglobin levels was  $6.88 \pm 2.30$  hours. For all

patients the average length of myoglobin elevation was  $23.6 \pm 7.41$  hours.

The serum half life of myoglobin calculated from the point of terminal descent from a logarithm of myoglobin vs time display was  $7.38 \pm 2.80$  hours.

#### Comparison of CPK infarct size with peak myoglobin and myoglobin time index

Infarct size as determined by CPK correlated relatively well with the peak myoglobin level ( $r = 0.98$ ,  $P$  less than 0.02) (Fig 1). The correlation between infarct size as determined by CPK and the area under the myoglobin concentration-time plot was excellent and highly significant ( $r = 0.98$ ,  $P$  less than 0.001) (Fig 2).

It is also of note that an infarct as small as 7.6 CPK-MB Eq is associated with an elevated serum myoglobin suggesting that an infarct at

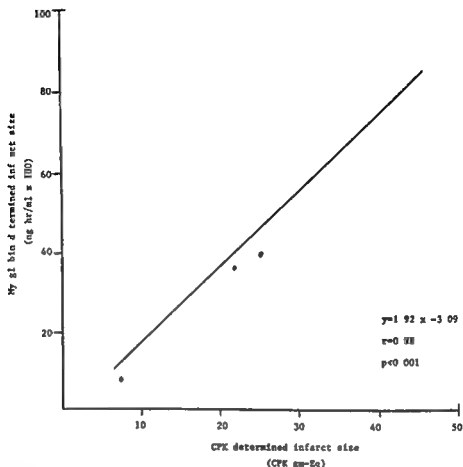


Fig 2 Correlation between myoglobin determined infarct size calculated from the area under the concentration time plot and CPH determined infarct size

least this small can be detected by an elevation in serum myoglobin

### Discussion

Myoglobin is a small molecular weight heme protein for which a quick and sensitive radioimmunoassay is available. Because of its rapid appearance there had been much enthusiasm for its use as a screening tool for acute myocardial infarctions. However, 50% of our patients with diagnostic ECG had normal initial myoglobin levels suggesting that despite its early appearance it may not be soon enough to warrant use as an emergency room screening tool. This agrees with the findings of others.<sup>11</sup> Myocardial and skeletal myoglobin cannot be differentiated and this lack of specificity also limits this use. A recent review<sup>12</sup> has discussed the causes of serum myoglobin elevation.

The purpose of selection of patients with Killip Class I infarctions for inclusion in this report was to minimize alterations in renal blood flow.

Although these patients remained without evidence of altered hemodynamics or reduced perfusion, the mechanism of cardiac myoglobin release and washout and the effects of changes in renal blood flow on myoglobin metabolism and clearance during myocardial infarctions are not known.

The results of myoglobin kinetics here reported are similar to previous studies<sup>13</sup> and confirm its rapid appearance and short half life after the onset of symptoms. In uncomplicated infarctions the mean time to first elevation was about 4 hours and a peak level occurred at about 7 hours after the onset of symptoms. The myoglobin remained elevated for an average of 24 hours with a mean half life being 7.4 hours.

As pointed out in another study,<sup>14</sup> most previous work relates the appearance and clearance time to hospital admission rather than the onset of symptoms. In one previous study when myoglobin were related to onset of symptoms, peak levels were shown to occur 6 to 8 hours later. We

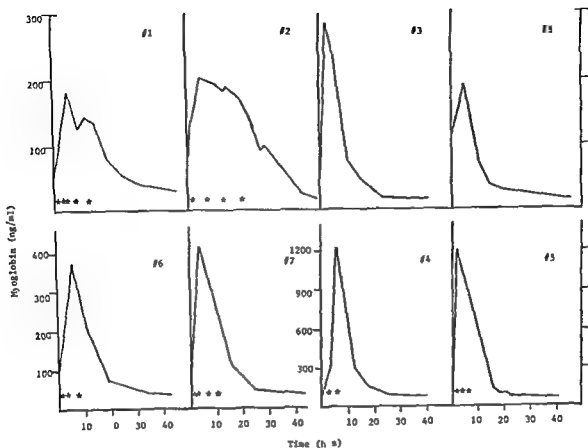


Fig 3 Serum myoglobin concentration time plot for each of the patients. Asterisks ( ) indicate time of onset of chest pain following admission

have also demonstrated that all infarcts in our group including one as small as 7.6 CPK gm Eq were associated with demonstrable increase at myoglobin levels. This suggests that even small infarcts are associated with detectable myoglobin elevation if serum collection is properly timed.

Comparison of infarct size as determined by standard CPK analysis with peak myoglobin levels seems to show some statistical significance. Although in experimental animals peak levels have shown an extremely high correlation with histologic infarction size following coronary ligation, this model of myocardial infarction may not completely resemble the clinical situation.

There is a highly significant correlation between infarct size as determined by CPK and that determined from a myoglobin time index by simply calculating the area under the concentration time curve. This suggests that myoglobin may be as good an indicator of infarction size as analysis of total CPK. Whether its usefulness in these uncomplicated infarctions is valid and may

be extended to complicated infarction deserves further study.

As has been reported and demonstrated by several markers, myocardial infarction is not an isolated event but may occur in separate episodes over hours or days.<sup>11</sup> Myoglobin by its rapid appearance and clearance is capable of separating further episodes of myocardial necrosis, as has been shown by Kagen and associates in the staccato phenomena of myoglobin release in myocardial infarctions. Within the first 48 hours of an infarction, conventional enzymes and evolutionary ECG changes prevent clear identification of post infarction chest pain as necrosis or reversible ischemia. The single spike pattern of myoglobin (patients No. 3 to 8) in Fig 3 probably indicates that the infarction occurred over a short period of time and further chest pain which did not produce further myoglobin elevation (patients No. 4 to 7) within the four hour symptom to myoglobin release period did not indicate further necrosis. However, a plateau period (pa-



tient No 2) or a second spike (patient No 1) suggests that the necrosis occurred over a longer period of time or occurred in several separate episodes.

### Conclusion

It has been shown<sup>11</sup> that myoglobin is one of the earliest appearing marker of myocardial infarction. However our results demonstrate that a single determination of serum myoglobin obtained within the first few hours of the onset of clinical symptoms may not be a sensitive test for the early detection of myocardial necrosis and may be negative in up to 50% of transmural infarctions. A level obtained at the time myoglobin was expected to peak (7 hours) might be more useful.

It is reported<sup>1</sup> that in animal studies peak myoglobin levels correlated well with histologic infarction size. In our study although correlation between CPK determined infarct size and peak levels exist the correlation between CPK determined infarct size and the myoglobin time index is much higher. Our findings suggest that this may be a simple alternate method for estimating the size of uncomplicated myocardial infarctions. Further studies are necessary before this data can be extrapolated to other clinical or hemodynamic subgroups of myocardial infarction.

Pain occurring in the 48 hours following first onset of symptoms is a common problem in the coronary care unit. Determining if this represents ongoing or repeated episodes of necrosis or reversible ischemia may be helpful in guiding therapy. Sequential myoglobin determinations suggest that not all episodes of postinfarction pain represent necrosis but some represent ischemia. Serial myoglobin levels because of their rapid appearance and clearance may be useful in following the progression or extension of an acute infarction.

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## Long-term results after aortic valve replacement with four different prostheses

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The ideal prosthetic heart valve should combine excellent durability, a wide opening laminar blood flow and minimal gradients; it should not traumatize blood cells or trigger thrombus formation. All these demands have so far not been fulfilled by any prostheses in spite of extensive research and development of new designs. In our hospital four types of aortic valve prostheses have been implanted during the seven year period from 1966 to 1973. First used was the Starr-Edwards ball valve type 1200 (SE 1200) with silicone rubber balls and metal cage which was later replaced by type 2300 in which a Stellite hollow ball moved within a cloth covered cage.<sup>1</sup> The modifications were done primarily to avoid ball variation<sup>2</sup> and escape<sup>3</sup> but also to reduce the high incidence of arterial thromboembolic complications which had been reported to accompany the oldest type.

The need for anticoagulation in patients with prosthetic heart valves had early been recognized; it reduced the incidence of arterial thromboembolism but only to some extent.<sup>4</sup> The incidence of thromboembolic episodes in our patients has previously been reported; it was found to be significantly lower with the newer modification of the ball valve but it still represented a serious problem in spite of adequate anticoagulation, cerebral embolism being the most frequent manifestation.

Increased red cell breakdown was found to accompany implantation of the ball valves and especially the SE type 2300 induced a considerable iron loss and in several patients frank hemolytic anemia.<sup>5</sup>

From 1971 disc valve prostheses have been used at this hospital. Two types were implanted: the Björk-Shiley (BS) and Lillehei-Kaster (LK)<sup>6</sup> prostheses both incorporating a free floating disc in an annular housing. The cage is slightly different in the two types; the LK prosthesis allows a wider opening and the disc closes against the ring while the BS disc has minimal contact with the housing and allows a very slight regurgitation.

The incidence of thromboembolic complications was however not lower after disc valve implantation than in patients with the SE 2300 prosthesis and thrombosis on the valve represented a particularly dangerous complication<sup>7</sup> as confirmed by others.<sup>8</sup> Red cell destruction was slight especially in patients with the BS prosthesis and hemolytic anemia did no longer represent a clinical problem.<sup>9</sup>

The present investigation was done in order to study the long term survival and clinical effect of valve replacement with the two types of Starr-Edwards ball valves and with the disc valve prostheses and to evaluate the influence of valve size on the clinical improvement.

### Materials and methods

Altogether 449 patients received isolated aortic valves during a seven year period from 1967 and 1973. Until November 1968 valve type SE 1200 was implanted in 80 patients; thereafter the modified valve SE 2300 was used in 173 patients.

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Table I Comparison of preoperative characteristics of patients receiving the different valve types

	Patients with valve type			
	SF 1700	SF 2300	LA	BS
No of patients	80	173	97	99
No of men	60	121	76	67
No of women	20	52	21	32
No in functional Group IV	17	42	30	31
No with arrhythmia	14	23	11	1
Mean age at operation (years)	1.3	1.26	53.3	54.6
Mean heart size (ml/M <sup>2</sup> )	1.12	661	6.0	604

Table II Preoperative hemodynamic findings in patients in the four groups

	No of patients with valve			
	SE 1200	SE 2300	LA	BS
Aortic stenosis				
Gradient 100 mm Hg	16	20	13	19
Gradient 50-99 mm Hg	6	14	18	18
Aortic incompetence				
Severe	19	20	37	34
Less severe	10	14	9	5
Aortic stenosis and incompetence	29	60	20	23
Mitral stenosis	3	3	4	3
Mitral incompetence	7	20	6	14
Mitral stenosis and incompetence	8	10	1	2
Coronary heart disease	6	16	10	12
Left ventricular aneurysm	1	2	2	3

From 1971 the BS and LK disc valves were inserted according to randomization in 196 individuals

Before operation a left side catheterization was always done in most patients by retrograde catheter introduction into the left ventricle and in some by transseptal catheterization. Angiography included contrast injections into the ventricle and the aortic root and pressures were recorded. Before 1970 selective coronary angiography was done in patients with angina, later also in patients older than 50 years. Thus coronary angiography was done in a larger proportion of the patients with disc than with ball valves.

The operative technique and postoperative care remained largely unchanged during this period of time but some important changes were later introduced which have reduced the early mortal

ity rate considerably. This is the reason why patients operated later were not included in the study. Oxygenation was achieved by a bubble oxygenator until 1970, thereafter a disc oxygenator with filters has been employed. Light hypothermia 32 to 34°C was routinely used and the left coronary artery was always perfused. The patients were heparinized with 300 IU of heparin per kilogram body weight and after operation the heparin activity was neutralized with protamine sulfate. Oral anticoagulation was started after two to four days unless bleedings persisted.

#### Follow up

The follow up examinations were performed at different times. The first examination of the patients with ball valves was done in the autumn of 1972 when all except six met up. Two years later the surviving patients were examined and only seven were unable to come.

Similarly the follow up studies of the patients with disc valves were done early in 1970 and in the autumn of 1976 six patients did not report for the first and 23 did not report for the last examination.

A questionnaire was sent to all patients physicians asking for additional information after each of the follow up examinations and relatives were contacted when necessary. When patients had been admitted to other hospitals requests for reports were sent. Thus the data presented were obtained from three different sources: hospital records, examination of the patients and information from doctors and relatives. None of the patients were lost for follow up.

At examination an exact history with emphasis on symptomatology and clinical course occurrence of arterial thromboembolic episodes or bleeding complications was obtained. A careful

clinical examination was done including ECG x ray of heart and lungs and several blood tests regarding intravascular hemolysis and anemia platelet function and coagulation including control of anticoagulant therapy with the Thrombotest as previously reported.<sup>11-13</sup> Heart size was calculated in milliliters per square meter of body surface area.<sup>14</sup>

Criteria for the diagnosis of arterial thromboembolism have been described earlier.<sup>15</sup>

## Results

The material is presented in Table I. More women received BS than LK valves in spite of randomization. The proportion of patients in functional Group IV according to the New York Heart Association (NYHA) classification differed only insignificantly between the patient groups being slightly higher in the patients with disc valves. Only minor differences appeared in the incidence of continuous arrhythmias, mostly atrial fibrillation, between the groups. The mean age at operation rose slightly throughout the period, mainly because some more individuals older than 70 years received disc valves than ball valves. The mean preoperative heart volumes were 188 ml/M less in patients with BS than in those with the SE 1200 valve. The differences were however not accompanied by similar deviations in the functional group distribution.

The preoperative hemodynamic findings are listed in Table II. No significant differences appeared in the distribution of severe stenosis with systolic peak gradients higher than 100 mm Hg or in severe aortic regurgitation with contrast reaching the apex of the left ventricle without being pumped out during the following systole or in the proportion of patients with combined stenosis and insufficiency. Mitral incompetence not regarded serious enough to require mitral valve replacement was more frequent in the BS than the LK group of patients while mitral stenosis was most common in patients with ball valves. Significant coronary artery stenosis or occlusion was found in approximately 10% of the patients.

The type of operation performed is presented in Table III. Mitral commissurotomy was more often done in patients with ball valves. This reflects a gradual change in policy regarding mitral valve operations with the preference of valve replacement for commissurotomy. Aortic

**Table III** Type of operations performed on the four patient groups

	Patient with valve type			
	SE 1200	SE 2300	LK	BS
Valve replacement alone	63	105	84	86
Valve + mitral commissurotomy	10	16	5	5
Valve + aortocoronary bypass			11	2
Valve + aneurysmectomy	1	1	2	11
Replacement of old valve			2	2
Emergency operations	6	11	8	9

**Table IV** Time from operation and to the first and second follow up studies in the four groups of patients

	Patients with valve type			
	SE 1200	SE 2300	LK	BS
Mean time to first examination (years)	4.7	2.7	2.5	2.5
Mean time to second examination (years)	6.7	4.7	4.3	4.3

coronary bypass was introduced at the hospital in 1970 but was performed only in five patients who simultaneously received disc valves. Resection of a left ventricular aneurysm was done in seven patients and in four previously implanted prostheses were replaced by disc valves.

The mean time intervals from operation until the follow up examinations are presented in Table IV demonstrating that the patients with the oldest ball valve type were followed on an average more than six and a half years and the patients in the three other groups were followed approximately four and a half years.

The long time survival calculated according to the actuarial method is illustrated in Fig. 1. The early mortality rate (deaths within 30 days) remained fairly constant at 15% throughout the period and did not differ between patients with disc and ball valves. The late mortality rate was remarkably similar in the four groups, the recorded or actuarial five year survival rate being 65% in patients with ball valves and 68% in those with disc valve prostheses. No significant differences

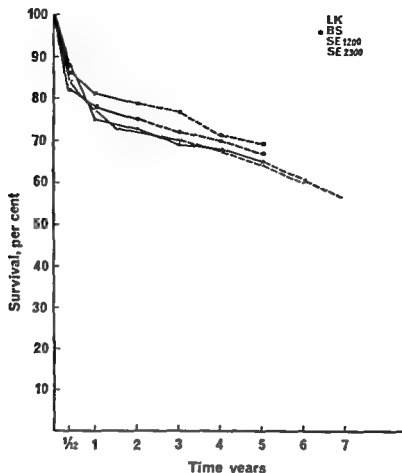


Fig 1 Long term survival after aortic valve replacement with the four different prostheses. The dotted lines indicate survival estimated by the actuarial method.

Table V Causes of late deaths after aortic valve replacement

	Patients with		
	Ball valves	Disc valves	Total
Myocardial failure	19	7	26
Arterial thromboembolism	6	3	9
Sudden death	6	3	9
Sepsis	5	1	6
Myocardial infarction	4		4
Intracranial bleeding	4		4
Mitral incompetence	1	2	3
Ventricular fibrillation	1	1	2
Reoperation	2		2
Rupture of aneurysm	1		1
Paravalvular leak	1		1
Cancer	2	2	4

appeared between any of the groups at any time.

The most frequent causes of early death were in this order: myocardial failure, arrhythmia, sepsis, myocardial infarction, and arterial thromboem-

Table VI Mean heart size before and after aortic valve replacement

	Mean heart size (ml/M <sup>2</sup> )			
	SE 1200	SE 2300	LA	BS
Before operation	679	63	649	584
At first follow up	584	586	617	543
At second follow up	619	615	59	567

bolism. Myocardial failure was responsible for an even higher proportion of late deaths, and also frequent was sudden death, as well as death from thromboembolic complications, mostly cerebral emboli in ball valve patients and valve thrombosis in the others (Table V). Myocardial infarction and intracranial bleeding caused some deaths in patients with prosthetic ball valves.

The heart size reduction from the preoperative examination until the first postoperative examination was most marked in patients with valve type SE 1200 who had the largest hearts before

**Table VII** Preoperative heart volumes in patients with isolated aortic valve disease who received smaller or larger valves

	Heart size (mL/M)			
	Smaller valves		Larger valves	
	Mean	S.D.	Mean	S.D.
SE 1200	545	143	719	168 p < 0.01
SE 2300	588	139	730	165 p < 0.001
LA	593	139	699	194 p < 0.07
BS	530	108	624	150 p < 0.01

operation but a significant reduction also occurred in the other groups (Table VI). From the first to the second follow up however no further over all improvement was found. The change in heart size in the individual patient may however not be due only to the type of valve implanted. Thus an increase in heart size was frequently seen in patients with coexisting valvular or coronary heart disease. In order to evaluate the effect of valve type and size patients with isolated aortic valve dysfunction were studied. The ball valve termed smaller were of size 10 A or less corresponding to an inner diameter of 15.5 mm in type SE 1200 and to 14.3 mm in series SE 2300 while the orifice diameter was 18 mm or less in smaller disc valves of both types. The preoperative heart size of patients who had the smaller valves of the different types implanted was on an average approximately 100 ml less than in those with larger valves (Table VII). At operation valve size had been selected according to the size of the aortic ostium. Implantation of the smaller ball valves of both series and especially type 2300 resulted in a very moderate reduction of heart size (Table VIII) and insertion of smaller disc valves also led to only a limited decrease in heart volumes. The disc valves did not represent an advantage over larger ball valves when reduction of heart enlargement is concerned. Indeed the most marked reduction was obtained with the larger valves of the SE 1200 series even if the orifice is considerably smaller than in the larger disc valves.

The mean functional group value was recorded according to the NYHA classification before and after valve replacement (Table IX). Most patients were in Functional Class 3. Individuals with disc valves were on an average in a slightly poorer clinical condition than the ball valve patients at the time of implantation. A consider-

**Table VIII** Relation between the orifice diameter of the implanted valve and the reduction of heart size from before operation to the second follow up examination

	Mean orifice diameter (mm.)	Reduction of heart size (mL/M)			
		Smaller valves		Larger valves	
		Mean	S.D.	Mean	S.D.
SE 1200	16.4	45.0	74.8	162.5	114.6
SE 2300	14.7	37.4	149.5	119.3	111.5
LA	18.2	56.0	120.3	174.4	163.9
BS	18.4	57.9	70.2	108.0	138.4

**Table IX** Mean functional group according to NYHA Classification before and after operation of patients who survived the follow up period

	Mean functional group			
	SE 1200	SE 2300	BS	LA
Before operation	3.18	3.18	3.31	3.36
At first examination	2.29	2.38	2.01	2.33
At second examination	2.34	2.31	2.29	2.42

**Table X** Preoperative functional group in patients with isolated aortic valve disease

	Functional group			
	Larger valves		Smaller valves	
	Mean	S.D.	Mean	S.D.
SE 1200	3.07	0.47	3.22	0.47 NS
SE 2300	3.08	0.47	3.26	0.5 NS
LA	3.29	0.51	3.12	0.53 NS
BS	3.35	0.54	3.29	0.53 NS

**Table XI** Relation between the orifice diameter of the implanted valves and clinical improvement expressed by NYHA group reduction

	NYHA group reduction			
	Smaller valves		Larger valves	
	Mean	S.D.	Mean	S.D.
SE 1200	0.67	0.88	1.09	0.33 NS
SE 2300	0.65	0.59	0.93	0.62 NS
LA	1.13	0.34	1.11	0.80 NS
BS	1.22	0.80	1.13	0.68 NS

able functional improvement occurred in all groups especially in patients with BS valves until the first follow up examination. The improvement seemed however to reach a maximum after a few years whereafter the condition remained constant or deteriorated slightly.

The preoperative functional impairment did not differ significantly between patients who received smaller or larger valves (Table X). The effect of valve size was evaluated in patients without other valvular defects or CHD (Table XI). Significant differences in the improvement which occurred in all eight groups did not appear although a slightly less marked positive development was recorded in patients with the smaller ball valves than with other types.

### Discussion

The early mortality rate after aortic valve replacement was similar in patients with the different valves indicating that prosthesis design was of little importance. The early death rate was comparable with<sup>1,2</sup> or higher than<sup>3</sup> that found by others and the most common causes of death were largely the same.<sup>1</sup> The majority of early deaths were due to complications unrelated to the prosthesis such as myocardial failure and arrhythmia indicating that the preoperative condition of the myocardium is of great importance for early survival. The early mortality rate was later been reduced considerably in our hospital chiefly because of improved techniques such as the introduction of extreme hemodilution during extracorporeal circulation, local cooling with out cannulation of the coronary arteries and better prophylaxis against ventricular arrhythmias.

Surprisingly even the late mortality rate appeared to be independent of valve type. Deaths caused by thrombus formation on the prosthetic valve such as cerebral embolism, valve dysfunction and sometimes myocardial infarction might to some extent be related to valve type and function. One would anticipate that the lesser orifice and higher peak systolic gradients across the ball valves especially the 2300 prosthesis would represent an extra load on the left ventricle and thereby carry a slightly worse prognosis than the disc valves. Again the importance of an adequate myocardial function for long term survival is evident as also reported by others.<sup>1</sup> An exact estimation of the mortality rate after aortic disc valve implanta-

tion can not be made since only nineteen late deaths occurred during the observation period which was shorter than in the groups of patients with ball valves where fifty three late deaths were recorded. Although a larger material could have provided a better basis for a comparison of late death rates our results allow the conclusion that the introduction of disc valves has not considerably reduced the late mortality rate after aortic valve replacement. The importance of myocardial function indicates that late survival can be better increased by earlier operations<sup>1</sup> than by improved design. Valve related causes of death such as arterial embolism or valve thrombosis might be reduced with combined anti thrombotic therapy where drugs affecting platelet function such as acetylsalicylic acid<sup>13</sup> or dipyridamole are added to anticoagulation.<sup>14</sup>

The moderate effect of aortic valve replacement on heart size is in accordance with the findings of others.<sup>1</sup> The maximum reduction appears to be obtained rather early after operation while no marked improvement can later be achieved regardless of valve type. Thus the preoperative heart size is the main determinant also for the postoperative size which again stresses the importance of myocardial function for the late results. The most marked reduction was found in patients with isolated aortic valvular lesions indicating that additional heart disease may negatively influence size and coexisting valvular coronary or other heart disease was the cause of the slight average increase in heart volumes from the first to the second examination.

The less favorable development of heart size in patients who received smaller valves instead of larger ones reflects the importance of a wide orifice in the implanted valve although part of the reduction observed can be explained by the preoperative heart enlargement. The minimal improvement in patients with smaller ball valves of series 2300 is in accordance with the high systolic gradients found across these valves. Surprisingly the larger disc valves did not appear to be superior to the ball valves even with regard to heart size reduction as would have been expected from the higher gradients across the ball valves in type 2300 in particular. Peak and mean systolic gradients are low across aortic disc valves especially the BS prosthesis and the heart volume reduction therefore does not fully

reflect the hemodynamic advantage of the BS prosthesis. Possibly the slight leakage in diastole through the disc valves particularly the BS prosthesis might have some influence. It appears however that an enlarged heart can be reduced only to a certain extent and that the condition of the myocardium is the limiting factor which determines the improvement that can be obtained even with the best prosthesis.

Similar considerations can be made regarding the clinical improvement that occurred. The patients with disc valves were on an average in a slightly poorer condition than those with ball valves as judged from the NYHA group classification. Functional class assessment is however subjective and the criteria are not equally easy to apply to all symptoms the patients experienced before operation: most frequently dyspnea and angina on exertion, fatigue and syncope. After valve replacement syncope no longer occurred, angina or dyspnea had disappeared or was less easily precipitated, while fatigue and dizziness were the most common complaints. These symptoms may be due to anesthesia or altered blood flow during operation, especially the effect of extracorporeal circulation. Continued microembolization may contribute or the symptoms may be unmasked by the disappearance of others.

The clinical improvement was considerable and corresponded to a reduction of one functional class in most patients, slightly less in those with ball than in those with disc prostheses. The clinical effect appeared to be greater than could be expected from the heart size reduction.

The considerable initial improvement did however not continue and a quite stable clinical condition was reached in most patients, while a slight deterioration was noted in several others. Even if a less favorable development often could be attributed to coexisting heart disease, the results indicate certain long term limitations to the effect of aortic valve replacement. The less pronounced clinical improvement in individuals with smaller ball valves, especially of type 2300, is in accordance with the minimal heart size reduction found and could be anticipated from the high systolic gradients across such valves. The equally satisfactory effect on functional capacity of larger and smaller disc valves and of larger ball valves indicates that the clinical course is less influenced by valve modifications than by myocardial function.

Although more sensitive criteria might reveal a clinical advantage of the hemodynamically better BS valves, our results suggest that more can be gained by earlier valve replacement than by further refinement of valve design.

### Summary

The long term results after implantation of isolated aortic ball and disc prostheses were studied. The Starr Edwards ball valve type 1200 was first used in 80 patients; thereafter type 2300 was used in 173. Later the Björk Shiley and the Lillehei Kaster disc valves were implanted in 99 and 97 patients according to randomization. The surviving patients with the oldest ball valve were examined after 4.7 and 6.7 years on an average; the others after approximately 2.5 and 4.5 years.

The early mortality rate was 15% and did not differ between the four groups. Even the late mortality rate was quite similar in the patient groups, the five year survival rate being 65% in patients with ball valves and 68% in those with disc valves as estimated with the actuarial method.

The average reduction of heart size was moderate and quite similar in the four groups, most pronounced in patients with isolated aortic valve involvement. The reduction was greater in patients who received larger rather than smaller valves of all types.

Aortic valve replacement resulted in a considerable clinical improvement in patients with all valve types; it corresponded largely to one functional group according to the NYHA classification. The heart size reduction and functional improvement was most moderate in patients with smaller ball valves, which could be anticipated from higher peak systolic gradients than across the other valves used. No significant differences appeared between patients with the larger valves of the four types.

The initial improvement, as recorded either by reduction of heart size or increase in functional capacity, had reached its maximum at the first follow up examination in most patients.

The preoperative myocardial function appeared to be the limiting factor which determined what late results could be obtained regardless of the type of valve implanted. The results therefore indicate that more can be achieved by earlier valve replacement than by improving the prostheses.



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## Crossed atrioventricular connections

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Some papers have been published recently about complex congenital heart diseases in which the cardiac connections are not associated with concordant or discordant atrioventricular relations. We named this type of malformation *crossed atrioventricular connections* (cross cross heart) which may be accompanied by different types of ventriculo arterial connections. Crossed atrioventricular connections have an anomalous position of the interventricular septum and the ventricles lose their usual position partially or totally and may become superior and inferior.

We have studied four cases of crossed atrioventricular connections: three concordant and one discordant. The visceral situs, the atrioventricular connections, the spatial position of the ventricles and the characteristics of the ventriculoarterial connections were analyzed.

We have reviewed the cases reported so far in the literature and propose a classification for this anomaly.

### Case reports

**Case No. 1** A 13 year old male patient was admitted in the hospital to diagnosis. There was a



Fig. 1 Frontal view of plain chest x ray. Observe the aorta (Ao) forming the left superior border of the heart. L = liver, S = stomach.

history of cyanosis since birth and moderate physical intolerance. A systolic diastolic cardiac murmur was heard along the left sternal border. The electrocardiogram revealed sinus rhythm, left axis deviation and biventricular hypertrophy. The chest roentgenogram showed an enlarged heart and increased pulmonary blood flow. The aorta formed the left superior border of the heart (Fig. 1). Cardiac catheterization revealed systemic pressures in both ventricles with identical pressures in the pulmonary artery. There was a significant right to left shunt.

Selective angiocardiograms were performed in the four cavities. The right atrial injection showed the right atrium to be in continuity with

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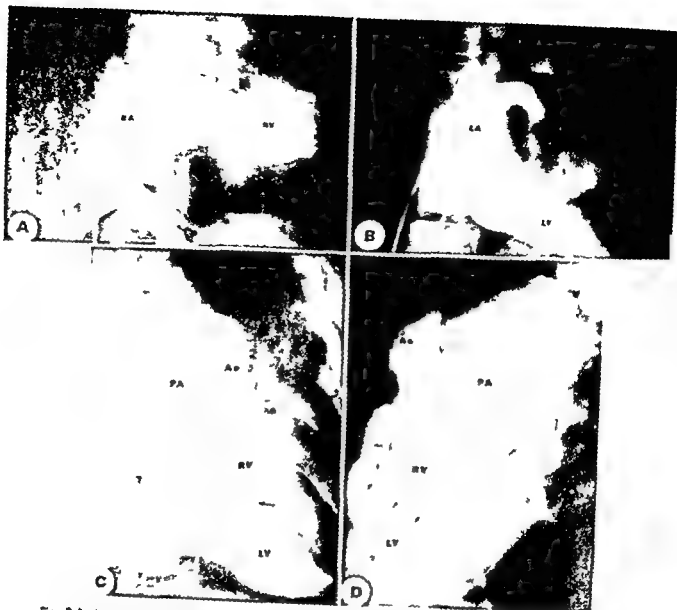


Fig 2 A through D Angiogram from a patient with situs solitus, concordant crossed atrioventricular connections and double-outlet right ventricle. A View showing right atrium (RA) with opacification of the right ventricle (RV) placed to the left and above. B Injection into the left atrium (LA) showing the left ventricle (LV) placed below. C Frontal view of right ventriculogram. Both great arteries are seen with the right atrium to the left of the enlarged pulmonary artery (PA). D The morphological left ventricle was opacified with contrast. The interventricular septum was horizontally oriented. The right ventricle and both great arteries were opacified by contrast. The left ventricular septal defect is outlined by the abnormal position of the septum that is outlined

the inflow portion of the right ventricle situated on the left and above (Fig 4A). The left atrium was connected to the left ventricle lying below (Fig 2B). The two ventricles were separated by an interventricular septum positioned in the horizontal plane. Both great arteries arose from the right ventricle with the aorta directed to the left of the pulmonary artery (Fig 4C and D).

**Case No. 2** A 4-month-old male patient was admitted with cyanotic congenital heart disease. Physical examination revealed a Grade 3/6 systolic murmur over the precordial area. There was moderate hepatomegaly. The chest x-ray film showed an enlarged heart and markedly increased pulmonary vascularity. The electrocardiogram suggested biventricular hypertrophy. Cardiac

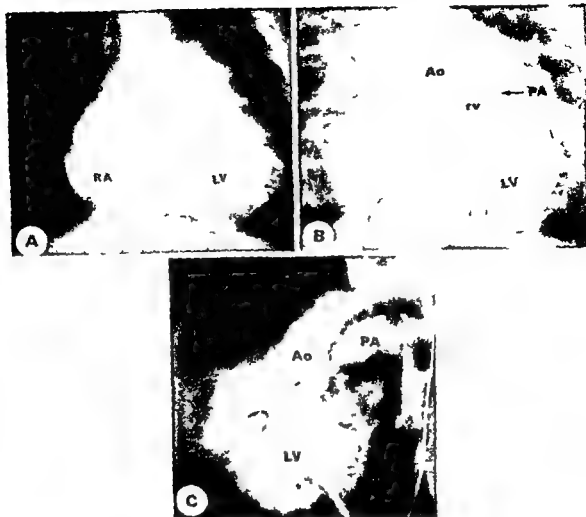


Fig 3 A through C Angiocardiogram from a case with situs solitus, discordant atrioventricular connections, and normally related and connected great arteries. A View of right atrium (RA) showing discordant atrioventricular connections. B Ventriculogram depicting left ventricle (LV). From this injection the hypoplastic right ventricle (rv) and both arteries were opacified. C Lateral view of left ventriculogram. The aorta (Ao) is arising from this ventricle. The small right ventricle is opacified via a ventricular septal defect (arrow).

catheterization was carried out. Systemic pressures were recorded in both ventricles and great arteries.

Biplane angiocardiograms were performed in both the right atrium and left ventricle. The right atrium was connected to the left ventricle (Fig 3A). Both great arteries opacified simultaneously. The main pulmonary artery was oriented from right to left (Fig 3B). In the lateral projection the left ventricle was posterior and inferior. The great arteries were normally connected and related (Fig 3C). The postmortem study revealed situs solitus with juxtaposition of both atrial appendages. The morphological right atrium drained to a morphological left ventricle situated on the left.



Fig 4 Frontal view of thoracic roentgenogram. The aorta (Ao) is forming the right superior margin of the heart. L = liver, S = stomach.

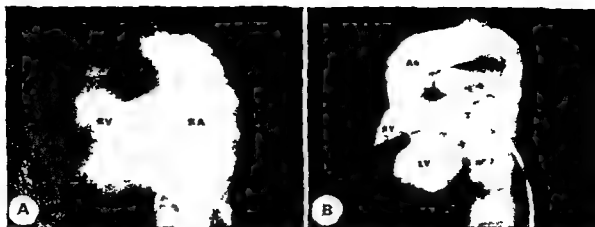


Fig 5 A and B Angiocardiogram from a patient with situs inversus, concordant crossed atrioventricular connections, and transposition of the great arteries. A: Injection into the right atrium (RA) with opacification of the morphological right ventricle (RV) well visualized in B B: Right ventriculogram. The catheter passed through the tricuspid valve (T). The right ventricle is small and the aorta (Ao) is arising from it. The morphological left ventricle (LV) placed below was opacified via a ventricular septal defect.

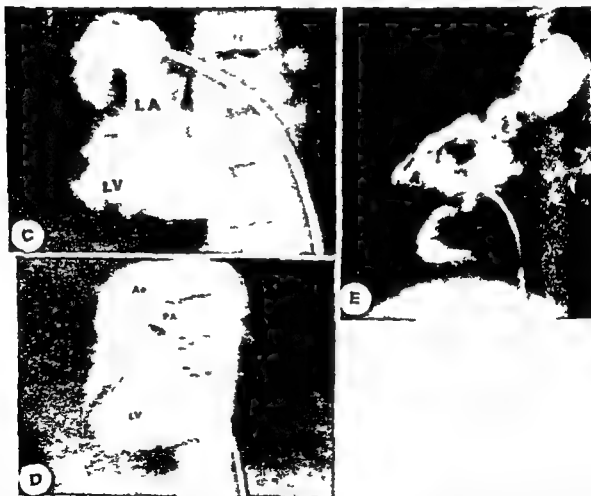


Fig 5 C, D, and E Angiocardiogram from same patient as in Fig 4 and B. C: Left atrium (LA) shows the connection of the catheter with the morphological left ventricle (LV). D: The left ventricle (LV) is well visualized and connected to the pulmonary artery (PA). Notice in E and D the anomalous position of the interventricular septum. E: Later film shows the abnormal position of the tricuspid valve (T) anterior and superior.

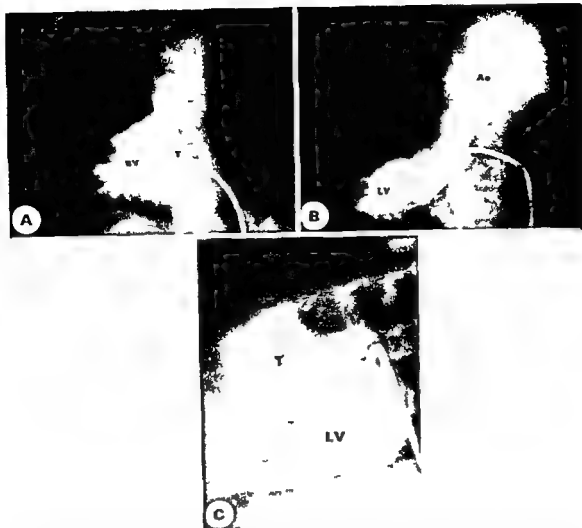


Fig 6 A through C A Right ventriculogram revealing the morphological right ventricle above and displaced to the right. The tricuspid ring has an abnormal position. B and C Frontal and lateral projections showing the inferior and posterior left ventricle (LV). Observe in C the abnormal relation between the posteroinferior mitral valve and anterosuperior tricuspid valve. (Compare with Fig 5E)

and below. The left atrium was connected to a hypoplastic right ventricle placed on the right and above. There was a membranous type ventricular septal defect. The arteries were normally related and connected with the pulmonary artery oriented from right to left.

**Case No. 3** A six year old boy had experienced cyanosis and cyanotic spells from the first year of life. Physical examination revealed the liver on the left and the cardiac apex to the right. There was a Grade 4/6 systolic ejection murmur in the second right intercostal space. The second heart sound was very loud in the same area.

The electrocardiogram suggested a situs inversus and right ventricular hypertrophy. Chest

x ray confirmed the presence of situs inversus and dextrocardia, normal cardiac size and a prominent right superior border formed by the aorta (Fig 4). Cardiac catheterization showed systemic pressure in both ventricles and the aorta.

Selective angiocardiograms were performed in both atria and in the right ventricle. The visceral situs inversus was noticeable (Figs 5A and C). The right atrium was connected to the right ventricle placed above (Figs 5A and B); the morphological left atrium was connected to the left ventricle located inferiorly (Figs 5C and D). The interventricular septum was horizontally oriented. There was transposition of the great arteries with an anterior and right sided aorta.

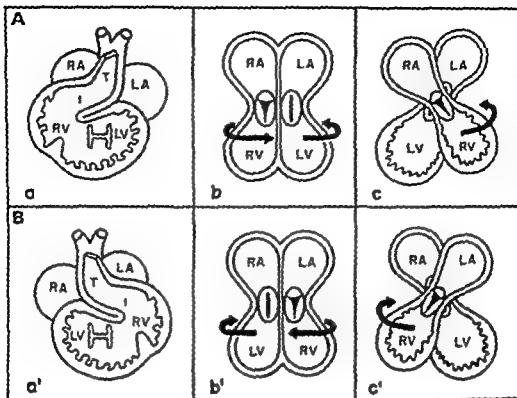


Fig 7 Diagrams of morphogenesis of crossed atrioventricular connections. Above a D-loop (a) establish concordant atrioventricular connections (b) before the abnormal rotation of both ventricles (c) Below an L-loop (a') which originates discordant atrioventricular connections (b') before the abnormal rotation of the ventricles (c) RA = morphological right atrium LA = morphological left atrium RV = morphological right ventricle LV = morphological left ventricle T = tricuspid M = mitral

Infundibular pulmonary stenosis and a ventricular septal defect were noticeable (Fig 5D). The tricuspid ring was anterior and superior (Fig 5E).

This patient underwent palliative surgery with a Blalock-Taussig anastomosis.

**Case No 4** In a seven year old boy moderate physical intolerance and late cyanosis were noted since he was 4 years of age. The liver was found on the left and the cardiac apex to the right. A continuous murmur was heard in the second right intercostal space and a systolic ejection murmur was heard in the third right interspace.

The electrocardiogram showed situs inversus and biventricular hypertrophy. The chest x-ray films confirmed the situs revealed discrete cardiomegaly and decreased pulmonary blood flow. Cardiac catheterization proved the same pressures in both ventricles and the aorta. The systolic pressure in the pulmonary artery was normal.

Biplane angiocardiograms were performed in both ventricles. The catheter was passed from a left sided right atrium into an anterior and

superior right sided right ventricle (Fig 6A). The morphological left ventricle had an inferior position (Fig 6B and C). The tricuspid and mitral valves had an almost anteroposterior relationship with the former slightly displaced to the right and above. The interventricular septum had an oblique direction. Both great arteries arose from the right ventricle with an anterior and left sided aorta.

## Discussion

Crossed atrioventricular connections are congenital heart malformations in which the spatial position of the ventricles is not in accordance with the position of the atria to which they are connected.

The connection would depend on a previous atrioventricular relation given by the type of bulboventricular loop. A concordant loop for a given type of visceral situs would end in a concordant connection while a discordant bulboventricular loop would end in a discordant connection.

In crossed atrioventricular connections an

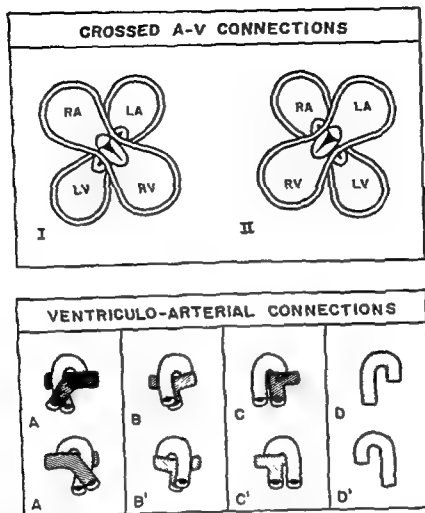


Fig 1 The diagrams I and II show concordant and discordant crossed atrioventricular connections respectively. Each one may be accompanied by all of the types of ventriculo-arterial connections shown below. A A Normally related great arteries B B Anterior aorta (transposed or malposed) C C Side by side great arteries (transposed or malposed) D D Persistent truncus arteriosus RA = morphological right atrium RL = morphological right ventricle LA = morphological left atrium LV = morphological left ventricle

abnormal rotation of both ventricles would occur after those connections were established moving both ventricles and their atrioventricular valves to the opposite side from their original position. In a case of situs solitus with concordant atrioventricular connections the morphologic right ventricle would rotate to the left with its atrioventricular valve while the left ventricle would move to the right also with its atrioventricular valve (Fig 7A). In situs solitus with discordant connections the right atrium is connected with the right sided left ventricle and the left atrium is connected with a left sided right ventricle afterwards the right ventricle rotates toward the right with its atrioventricular valve and the left ventricle would turn to the left also with its atrioventricular valve. The tricuspid

valve crosses in front of the mitral valve as it does in cases with concordant connections (Fig 7B). For situs inversus we would have the mirror image of the process observed in situs solitus either with concordant or discordant connections.

The horizontal position of the interventricular septum can be explained by a lack of descent of the right ventricle previous to its ventro medial rotation.

Up to this time there are 36 cases reported in the literature of which 30 were in situs solitus and one with visceral heterotaxia.

From our own material two cases were in situs inversus both with concordant atrioventricular connections. From the 40 reported cases including ours 27 had concordant connec-



Table 1 Crossed atrioventricular connection

Atrioventricular connection	Ventriculo-arterial connections
A Concordant	Normally connected great arteries Anterior aorta (trans or malposed) Side by side great arteries (trans or malposed)
B Discordant	Double-outlet right ventricle Double-outlet left ventricle Single outlet

Situs solutus of inversus

tions and 13 were discordant.

There are different types of ventriculo arterial connections such as in other congenital heart malformations. The most common is transposition of the great arteries in its various forms less frequently double outlet right ventricle pulmonary atresia, normally related great arteries as Case 2 of Sieg and associates and the second of our own series and finally side by side great arteries.

There has not been described any case with persistent truncus arteriosus (Figs 8 I and II D and D). We may expect cases with isolated crossed atrioventricular connections (Figs 8 IA and II A) in which the spatial position of normally related great arteries does not correspond to the spatial position of the ventricles as in isolated ventricular inversion described by Van Praagh and Van Praagh.

If we consider the visceral situs and the atrioventricular connections we may classify these cardiac malformations into two separate groups one concordant and one discordant and we can expect that each one may be associated with different types of ventriculo arterial connections either with single or double outlet ventricle (Table 1).

Cross-cross hearts are with rare exception complex congenital heart malformations and for this reason they are difficult to diagnose. The type of atrioventricular or ventriculo arterial connections and the presence or absence as well as the degree or size of pulmonary stenosis or septal defects will be responsible for the clinical and hemodynamic pictures. Most of the published cases show transposition of the great arteries associated with septal defect and pulmonary stenosis so we can find early cyanosis and symp-

tomatology very common in those congenital heart malformations with decreased pulmonary blood flow.

The x ray films are not of great value. We have observed the aorta on the left in situs solutus or on the right in situs inversus. These findings suggest that the great arteries are not in their usual place. The abnormal situation of the aorta suggests a complex anomaly. This condition with crossed atrioventricular connection should be included in the differential diagnosis along with corrected transposition of the great arteries, some forms of double outlet right ventricle and malposition of the great arteries.

Atrioventricular connections were determined in three cases by means of the right and left atriangrams. In the first two the morphological right ventricle was situated on the opposite side while the left ventricle was located below. In the third case discordant connections were established when the left ventricle was opacified in the opposite side and below.

In the fourth case it was observed that the tricuspid and mitral valves had an almost anteroposterior relationship with a moderate displacement of the former to the right an unusual position for this type of visceral situs. When we compare the position of the ventricular cavities with the other case in situs inversus we observe the existence of various degrees of ventricular rotation. In this case the interventricular septum had an intermediate position because of a partial rotation of the ventricles. This finding supports the existence of an abnormal rotation after septation.

Due to the morphologic features of this cardiac anomaly the systematic diagnosis of congenital heart malformations has been reviewed. Its nomenclature was based primarily on relations and more recently on connections. In situs solutus a D loop indicated that the right ventricle was on the right and an L-loop situated the right ventricle on the left. After the reports of cross-cross hearts we may conclude that this type of bulbous ventricular loop produces atrioventricular connections regardless of the final spatial position of the ventricles.

The importance of the type of loop is seen when we consider that most of the cases with cross-cross hearts show concordant connections just as in other cardiac malformations without "cross" type of atrioventricular connections.

When we consider the rules for localizing the ventricles by means of the position of the great arteries<sup>1</sup> these become difficult to apply when the ventricles are not in their usual right and left position. For this circumstance the presence of either a right or a left sided aorta makes the localization of its corresponding ventricle(s) difficult. These rare but distinctive anatomic relationships with crossed atrioventricular connections with unusual spatial orientation of the ventricles are of theoretic importance because they are exceptions to the rules for systematic diagnosis of congenital cardiovascular anomalies.<sup>1</sup> Moreover they are of clinical significance when surgical repair is considered.

## Summary

Four cases of crossed atrioventricular connections are described. All of them were diagnosed at cardiac catheterization by angiocardiography and one was examined pathologically. Two possessed situs solitus one with concordant connections and the other with discordant connections; the other had two situs inversus both of them with concordant connections. Two had double outlet right ventricle one had transposition of the great arteries and the other had normally related and connected great arteries. These cases have been interpreted as representing abnormal rotation of the ventricles following septation. A review of 36 cases previously reported on and our own cases suggests that most patients have concordant atrioventricular connections. There are many types of ventriculoarterial connections, the most frequent being transposition of the great arteries. There has not been any case reported with persistent truncus arteriosus. On the basis of atrioventriculoarterial connections we propose a classification for this malformation. We discuss the importance of the bulboventricular loop in the type of atrioventricular connections, some clinical implications for the diagnosis and analyze the value of the rules to localize the ventricles by means of the position of the great arteries.

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# Clinical characteristics, electrocardiographic and enzyme correlations, and long-term prognosis of patients with chest pain associated with ST depression and/or T wave inversion

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The electrocardiographic distinction between transmural (TMI) and nontransmural myocardial infarction (NTMI) although not always accurate at autopsy has been used by clinicians to assess the clinical severity and prognosis following the coronary event. Previously the prognosis of TMI as diagnosed by the electrocardiogram (ECG) has been considered to be graver than that of NTMI. Recent reports however indicate that patients suffering NTMI may experience complications similar to TMI and a long term prognosis that is equal to or worse than TMI. This retrospective study was undertaken to provide further information about the clinical course, electrocardiographic and enzyme correlations, and long term prognosis of patients admitted with prolonged chest discomfort and serial ST and/or T wave changes consistent with commonly used criteria for nontransmural myocardial infarction.

## Methods

The hospital records of 90 patients dying or discharged with the final diagnosis of nontransmural or subendocardial myocardial infarction

during the period from March 1971 to November 1976 were reviewed in detail. From these charts 50 patients were found to meet the following criteria:

1 *Chest pain* or discomfort consistent with myocardial infarction lasting 30 minutes or more and occurring within 24 hours of admission.

2 *ECG Changes* (a) New ST segment depression of the ischemic or square wave type of at least 1.0 mm occurring in two or more leads and persisting at least 24 hours and/or (b) New T wave inversion in two or more precordial or frontal plane leads persisting at least 24 hours (c) ST T or T wave evolution during hospitalization (d) No evidence by ECG of transmural infarction as defined by the development of an abnormal Q wave.

3 Patients with either complete left bundle branch block or Estes criteria for probable or definite left ventricular hypertrophy were excluded. In addition patients with electrolyte disturbances or stroke were not included.

4 Patient survival for 24 hours to allow for at least two ECG's at least 24 hours apart.

Prior cardiovascular history was obtained from review of physician and nurses notes; a cardiovascular data base compiled on each patient on admission; previous admission records; physician office records; and in most cases by patient interview at the time of follow up. July 1978. Patients were considered to have stable angina pectoris if they had symptoms consistent with transient myocardial ischemia occurring for at least one month or more. Unstable angina was

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**Table I** Age and sex distribution of patients studied

Age (yrs)	Male	Female	Total (n)
40-49	2	1	3 (6)
50-59	3	2	5 (10)
60-69	11	7	18 (36)
70-79	10	10	20 (40)
80-89	1	3	4 (8)
Total (n)	27 (54)	23 (46)	50 (100)

**Table II** Clinical history

Historical parameter	Number of patients	(%)
Asymptomatic	10	(20)
Angina pectoris chronic stable	9	(18)
Angina Pectoris chronic unstable	21	(42)
Angina pectoris recent onset (<4 weeks)	10	(20)
History of prior myocardial infarction	22	(44)
History of congestive heart failure	8	(16)
History of hypertension	25	(50)
History of cigarette smoking (>1 pack/day)	19	(38)

as any combination of the following (a) onset of angina pectoris within one month of admission (b) episodes of angina pectoris during the month prior to admission that were more frequent more severe more easily precipitated more prolonged or that occurred at rest

Each patient was followed closely by a cardiologist a cardiologist fellow a personal physician and by experienced CCU nurses. A data sheet was used to compile a clinical profile of the illness and the complications as they occurred. In this fashion detailed observations were made on each patient by the physicians and nurses a minimum of five times a day. Twelve lead electrocardiograms were recorded at the time of admission and daily while the patient was in the coronary care unit (CCU). After discharge from the CCU the frequency was variable but all patients had at least one further electrocardiogram near the time of discharge. At the time of admission the precordial electrocardiographic electrode positions were

**Table III** Clinical parameter during hospitalization

Clinical parameter	Number of patients	(%)
Uncomplicated hospital course	23	(46)
Uncomplicated hospital course	27	(54)
Congestive heart failure	16	(32)
Shock	2	(4)
Positive enzymes	37	(74)
Ventricular tachycardia	5	(10)
Ventricular fibrillation	6†	(12)

One of these patients died

†In four patients this was a terminal rhythm

marked with indelible ink to insure reproducibility. Old electrocardiograms were available for 90% of the patients either from prior admissions or from office records. Blood was drawn on admission and each morning thereafter for at least three days for determination of total serum creatinine phosphokinase (CK) and total lactic dehydrogenase (LDH) enzymes. A review of the emergency room and CCU records showed that none of the patients had received intramuscular injections. A patient was said to have positive enzymes if the total CK and/or LDH values displayed a rise and fall and the highest value exceeded the upper limits of normal. In addition the highest value had to exceed the lowest value by at least twofold.<sup>1</sup>

### Hospital course

**1 Uncomplicated course** Relief of pain during the first 24 hours without recurrence absence of complex atrial and/or ventricular arrhythmias absence of or only lower lobe rales and/or a ventricular gallop that disappeared

**2 Complicated course** Recurrent or persistent ischemic pain after the first 24 hours requiring therapy arrhythmias requiring extended periods of therapy slowly clearing persistent or recurrent congestive heart failure cardiogenic shock cardiac arrest

On follow up by review of office records subsequent hospital records or telephone interview July 1978 a patient's status was considered asymptomatic if no or rare angina had been experienced. A death was considered to be of cardiovascular etiology if it was known to occur in the setting of chest pain or was sudden. When circumstances surrounding the death were either unknown or not clearly related to a cardiovascular

Table IV Correlation of electrocardiographic changes enzymes curves and course during hospitalization and follow up

	T wave inversion		ST depression		Mixed changes		Total	
Incidence (% of total)	20 (40%)		1% (2%)		18 (36%)		38	
Limb leads alone	1		0		0		1	
ECG changes V leads alone	5		2		2		9	
Both limb & V leads	14		10		16		40	
	+Enzymes	-Enzymes	+Enzymes	-Enzymes	+Enzymes	-Enzymes	+Enzymes	-Enzymes
Number (% of Group)	11 (55%)	8 (45%)	10 (83.3%)	2 (16.7%)	16 (88.9%)	2 (10.1%)	37 (74%)	13 (26%)
CHF at time of admission	3	3	4	0	6	0	13	3
Shock during hospitalization	0	0	1	0	1	0	1	0
Died during hospitalization	0	0	4	0	0	0	4	0
Uncomplicated hospital course	8	5	3	2	8	1	19	8
Complicated hospital course	3	4	7	0	8	1	18	5
MI after discharge	4	1	0	0	3	0	7	1
Angina during follow up	6	5	2	0	7	0	15	5
Died during follow up	5	2	9	1	8	1	15	4
CV death	4	1	0	1	6	0	10	2

lar etiology the cause of death was considered unknown. A patient was counted as having suffered subsequent myocardial infarction (MI) if this was documented by a review of hospital records, electrocardiograms and enzyme studies.

## Results

**Population studied (Table I)** There were 27 males (54%) and 23 females (46%). The majority of patients (76%) were in their sixth or seventh decades. The ages ranged from 43 to 88 years with a mean of 68.3 years and a median age of 69 years. The mean hospital stay was 17.4 days with a range of one to 43 days.

**Prior cardiovascular history (Table II)** Thirty patients (60%) had a history of chronic angina pectoris and ten other patients (20%) developed angina pectoris for the first time during the four weeks prior to admission. Twenty-two patients (44%) related a history of prior MI. 21 of whom also had a history of chronic angina pectoris. In all 40 patients (80%) had a history of symptomatic coronary artery disease (CAD). In eight patients (16%) there was a history of CHF treated with digitalis. These eight patients also had a history of chronic angina pectoris and at least one prior MI. Excluding the 10 patients with recent onset of angina pectoris the duration of chronic angina pectoris ranged from two months to 30 years with a mean of 6.3 years. Thirty-one patients (62%) had unstable angina pectoris. In 21 (42%) it was manifested by a change in pattern of chronic angina

pectoris and in ten (20%) by angina pectoris of recent (less than 4 weeks) onset.

**Five of the infarctions occurred in patients who were hospitalized and recovering from recent (less than 10 days prior to MI) noncardiovascular surgery.** Four of these five patients related a history of prior MI and chronic angina pectoris. Two of these five patients suffered cardiac arrest with their recurrent MI and one died. One patient in this group of five died during hospitalization because of severe heart failure.

**Hospital course (Table III)** Sixteen patients (32%) had CHF on admission. Six of these patients had a history of CHF. 11 had a history of at least one prior MI and 15 had a history of chronic angina pectoris. Two patients were in shock on admission and both died during hospitalization. One patient developed shock on the second hospital day and died. There were 37 patients (74%) with positive serum CK and/or LDH enzyme curves. Two patients with positive enzymes died on the second hospital day and therefore a complete curve showing rise and fall of enzymes could not be obtained. In one of these two the CK value rose nearly twentyfold from a normal value on the second hospital day. In the other the CK value doubled by the second hospital day with an increase in the MB isoenzyme fraction. In five patients ventricular tachycardia was recorded during their CCU stay. One of these patients subsequently died in ventricular fibrillation. In the other four the rhythm spontaneously

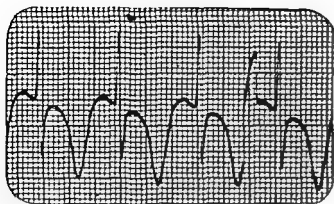


Fig 1 Lead V illustrating deep symmetrical T wave inversion pattern

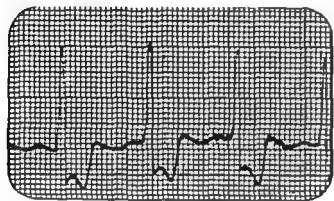


Fig 2 Lead V illustrating deep ST segment depression pattern

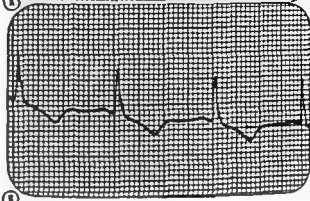
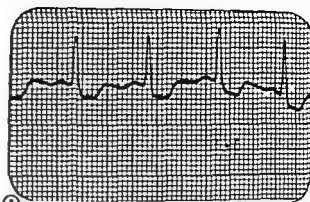


Fig 3 A and B Two examples of mixed ST and T wave changes in limb Lead II

striking and tended to fall into three major categories

1 Twenty patients (40%) had serial electrocardiograms with predominantly deep T wave inversion (Fig 1). These changes were often quite marked with T waves changing from upright or isoelectric to as deep as 15 mm in some precordial leads. These changes were usually recorded in both the precordial and the limb leads. The inverted T waves nearly always had symmetrical limbs and were frequently the most deeply inverted in the mid precordial leads. Occasionally the ST segments in those leads destined for deep T wave inversion on subsequent ECGs were transiently depressed at the time of admission but usually became isoelectric within 24 hours. Eleven of the 20 patients (55%) showing this particular ECG change (deep T wave inversion) had positive enzymes. None of these patients died during hospitalization.

2 Twelve patients (24%) had serial ECG changes primarily involving ST segment depression. This was also most frequent in both the chest and limb leads. Changes were often striking with ST segment depression of 8 to 10 mm in some cases (Fig 2). The ST segment was either

converted to sinus rhythm and did not recur after treatment. Six patients exhibited ventricular fibrillation. In four cases this was a terminal rhythm. Two patients were successfully defibrillated without subsequent cardiac arrest or death during hospitalization.

Patients were retrospectively assigned to one or two hospital courses as outlined in the method section. Twenty-seven patients (54%) had an uncomplicated hospitalization whereas 23 (46%) had a complicated course. Ten of the 19 patients who died during the follow-up period of one to 82 months (mean 33.4 months) had complicated hospital courses.

No patients experienced clinically detectable pulmonary or systemic emboli or pericarditis. No patients developed a recognized rupture of the ventricular septum or papillary muscle.

**ECG changes (Table IV)** In all 50 patients the ECG changes persisted for at least 24 hours and showed evolution during the hospitalization. Electrocardiographic changes were frequently

Table V Clinical features and hospital course in patients who died during study

	All patients	Died during hospitalization	Died during follow up		
			Cardiovascular causes	Unknown causes	Noncardiovascular causes
Number of patients	50	4 (8%)	12	5	■
Average age at time of NTMI	68.3	67.0	70.9	70.3	72.0
History of prior MI (%)	22 (44%)	4 (100%)	5 (41%)	4 (80%)	0
History of angina pectoris (%)	40 (80%)	4 (100%)	8 (66%)	5 (100%)	■
CHF with NTMI (%)	16 (32%)	1 (25%)	3 (25%)	3 (60%)	1 (50%)
+ Enzymes (%)	32 (74%)	4 (100%)	10 (83%)	4 (80%)	1 (50%)
T inversion pattern (%)	20 (40%)	0	5 (41%)	1 (20%)	1 (50%)
ST-depression pattern	12 (24%)	4 (100%)	1 (8%)	2 (40%)	0
Mixed pattern	18 (36%)	0	6 (50%)	2 (40%)	1 (50%)
Uncomplicated hospital course	27 (54%)	0	9 (75%)	0	0
Complicated hospital course	23 (46%)	4 (100%)	3 (25%)	5 (100%)	■ (100%)

Sudden death MI CHF

isoelectric or downsloping and depression occurred most frequently in the lateral precordial leads and in limb Leads I and aVL. In those leads showing significant ST depression the T waves were usually inconspicuous and biphasic or slightly inverted. As with the deep T inversion pattern serial electrocardiograms showed slow resolution of these changes over a week or more. Ten of these 12 patients (83.3%) had positive enzymes. All four of the patients who died during hospitalization had this ECG pattern. Two patients died on the second hospital day, one died on the sixth hospital day and one patient died on the seventh hospital day. All four had positive enzymes, a history of prior MI and a history of hypertension.

3. Eighteen patients (36%) had ECG changes involving both the ST segment and the T wave similar to those described above. Usually, however, the changes were much less marked than when the changes were confined to either the ST segment or the T wave alone (Fig. 3). As with the other two patterns described above, this mixed pattern was found to be most frequent in both the limb leads and the chest leads. In this group 16 of the 18 patients (88.9%) had positive enzymes. None of this group died during hospitalization.

Several clinical parameters from those patients with acute infarction in hospital as well as several findings on follow up were looked at in relation to the major ECG patterns manifested with NTMI (Table IV). As noted, the four in-hospital deaths all occurred in patients who had deep, persistent ST depression. There was no statistical difference

in the incidence of a complicated hospital course in the three groups, although it tended to be lower (35%) in the group with T wave changes alone than it was in the group with ST segment changes (58%) or mixed changes (50%). There did not appear to be any relation between the post-hospitalization course and the ECG changes manifested during hospitalization (Table V).

**Follow up.** Forty-six patients survived hospitalization. One was completely lost to follow up after discharge. Two patients were lost after 16 and 40 months of follow up. The remaining 43 patients (93.5% of those discharged) were followed for one to 82 months (mean of 33.4 months and median of 33.0 months).

Among the 45 patients partially or totally followed up, there were eight myocardial infarctions during follow up, occurring one week to 34 months after discharge. Six of these occurred within 3 months following discharge. Of the eight patients with MI following discharge, two patients had recurrent nontransmural MI by electrocardiogram; one patient died in the emergency room with an extensive transmural infarction at autopsy and one patient was hospitalized elsewhere with a diagnosis of myocardial infarction and cardiac arrest.

At the time of follow up, 11 of the 24 patients (45.8%) still alive had angina pectoris. Nineteen of the 43 patients completely followed up (44%) had died during follow up. Twelve of these deaths were known to be due to cardiac causes. In five



patients the cause of death could not be determined. One patient died in an automobile accident and one died from cancer of the prostate. Of the 12 patients whose death was due to cardiovascular disease, eight died suddenly at home. Two of these 12 patients died during hospitalization for myocardial infarction (one NTMI and one TMI) and two died from refractory congestive heart failure while hospitalized. The average age at the time of NTMI of the 19 patients who died posthospitalization was 70.9 years. From the group of 12 patients who are known to have died from cardiovascular causes after discharge, four died during the first year of follow up, three died during the second year, two died during the third year, and three died between the fourth and sixth years of follow up. The longest survivor among this group of 12 patients died 67 months after the NTMI. There was a statistically significant greater incidence of both angina pectoris and myocardial infarction during follow up in those patients who manifested a positive enzyme curve during hospitalization with NTMI. Similarly, there was a greater incidence of death from all causes, including cardiovascular death, during follow up in those patients manifesting positive enzyme curves compared to those patients without positive enzyme curves (Table IV).

### Discussion

Advances in the diagnosis and therapy of coronary atherosclerotic heart disease have given impetus to studies that help define the clinical characteristics and prognosis of various subsets of this disease. Until recently, NTMI was felt by some to represent a mild form of myocardial infarction with a relatively good prognosis. The reasons for this optimistic view are unclear and may be based upon the more impressive visual impact of ST segment elevation and the development of abnormal Q waves as compared to ST segment depression and/or T wave inversion alone. In fact, the electrocardiogram may be deceiving since transmural infarction may occur despite ECG changes pointing to a subendocardial localization. In addition, the ECG may not reveal the presence of prior infarction reinfarction in areas of prior infarction or infarction in certain areas of the heart. For these reasons, we prefer to use a clinical taxonomy referring to these patients as "prolonged pain with objective evidence of infarction with or without complication." This approach utilizes the information

that is available to the clinician and helps to avoid erroneous assumptions. The group can then be further defined on the basis of electrocardiographic alterations.

The patients reported here represent a population defined by prolonged chest pain compatible with myocardial infarction occurring within 24 hours of admission, survival for at least 24 hours to insure that the ECG changes do not suggest transmural involvement and ECG changes thought to represent nontransmural infarction. Since the majority of hospitalized patients with acute myocardial infarction who die do so within 24 hours, this study is slanted towards a relatively high hospital survival group with a low incidence of cardiogenic shock. The purpose of this study was to analyze this selected group in terms of hospital course, enzyme correlations with ECG changes, and posthospitalization prognosis. Our findings are similar to other recently reported studies and suggest the following conclusions:

- 1 NTMI occurs most often in patients with known coronary artery disease. A prior history of angina pectoris and/or myocardial infarction was obtained in 80% of our patients. Thirty-one (62%) patients had unstable angina pectoris prior to admission and despite intensive medical therapy, in most developed NTMI. Other studies comparing the clinical features of TMI and NTMI have suggested that a prior history of angina pectoris is greater with NTMI.

- 2 There was a high incidence of heart failure, hypotension, life-threatening arrhythmias, and recurrent ischemic pain during hospitalization for NTMI. Five of our patients had ventricular tachycardia and six had ventricular fibrillation. A third of our patients developed congestive heart failure by examination and/or chest x-ray. Other studies confirm that NTMI and TMI share a similar in-hospital incidence of arrhythmia, CHF, shock, and death.

- 3 There was an 8% hospital mortality rate and a high incidence of recurrent myocardial infarction and death in the next several years. This compares to a hospital mortality rate of 7% in 200 consecutive patients with transmural infarctions surviving at least 24 hours after CCU admission during 1971 to 1973 at Piedmont Hospital. In the present study during follow up over a mean period of 33.4 months, there was a further mortality rate of 45.2%. In addition, 17.8% of the discharged patients in the present study suffered a subsequent myocardial infarction and in three fourths

of these patients the myocardial infarction occurred within 3 months of discharge. A high mortality rate and sudden death during follow up has been a feature of other studies of NTMI.<sup>6</sup> A study by Cannon and associates<sup>7</sup> comparing the posthospital course of TMI and NTMI found that the NTMI had a higher incidence of sudden death (33% vs 15%), cardiac related mortality rate (41.6% vs 24.3%), recurrent MI (26% vs 12%) and angina pectoris (61% vs 36.2%) over a 36 month mean follow up period.<sup>7</sup>

4. There may be a more benign initial course in patients with only T wave inversion. Our patients with ECG changes confined primarily to deep T wave inversion had a lower incidence of enzyme elevation, CHF, serious ventricular arrhythmias and major problems during hospitalization although the differences were not statistically different. Their hospital mortality rate was 0% as compared to four deaths (33.3%) in the group with persistent deep ST segment depression. Lown and co-workers have also reported 0% mortality rate in 50 patients with T wave inversion only as compared to a 27.6% mortality rate in 29 patients with ST segment depression. Abbott and Scheinmann<sup>11</sup> also found a higher incidence of shock and death with ST depression than with T wave inversion only. No statistically significant correlation was apparent between the major ECG changes manifested with the NTMI and the posthospitalization course in the present study. This may be explained by other studies that show that the prognosis may be dependent upon the severity, location and extent of the coronary artery obstruction and the extent of new and old myocardial damage.

5. We found an over all incidence of positive enzyme curves of 74% in the 50 patients. Further analysis showed that the group with T wave inversions had a 55% incidence, the group with primarily ST segment depression had an 83.3% incidence and the group with the mixed ECG pattern had an 88.9% incidence of positive enzymes (Table IV). This may be explained on the basis of a smaller amount of myocardial necrosis occurring in the group with T wave inversion alone or the possibility that some patients in the group with T wave inversions did not actually suffer any myocardial necrosis. This group did have fewer hospital complications and no hospital deaths however the posthospitalization course was similar to the other ECG groups. Rapaport<sup>12</sup> has recently discussed the problem of

persistent ST-T wave changes with serial enzymes remaining in the normal range. He suspected that many of these patients had had small nontransmural myocardial infarctions.

6. Other studies have shown that patients with NTMI usually have severe coronary artery disease.<sup>1</sup> Recent studies of the coronary arteriograms of survivors of NTMI have found a high incidence of multivessel disease. All six patients autopsied in our series had extensive coronary atherosclerosis.

In summary, nontransmural myocardial infarction is not a mild myocardial infarction. Studies showing a similar hospital course and mortality rate for patients with TMI and NTMI support the concept that it is the extent of the coronary atherosclerosis and myocardial dysfunction from old and new infarctions rather than the ECG classification that primarily determines prognosis. A recent study by Strauss and colleagues<sup>13</sup> concluded that the predominant determinant of mortality was infarct size regardless of whether it was subendocardial or transmural. Because of the significant incidence of further myocardial infarction and death and the documentation that severe multivessel disease is often present, early coronary arteriography may be indicated. This decision must be carefully considered because of the advanced age (average age 68.3 years in our study) and the unknown surgical prognosis in this group of patients. A recently reported study of 28 patients with subendocardial infarction followed by saphenous vein aortocoronary bypass grafting within 3 months of the infarction has shown a 10.7% incidence of perioperative infarction, a 3.6% operative mortality rate and no late deaths or recurrent infarction at a mean follow up period of 16 months.<sup>14</sup> This study, however, excluded patients over age 70 and should not be extrapolated to an older age group. In another recent study reporting the long term results of 28 patients subjected to coronary bypass surgery during the acute phase of NTMI there were no hospital or late deaths during a mean follow up period of 29 months and a majority of patients demonstrated functional improvement.

### Summary

The clinical characteristics, electrocardiographic changes and long term prognosis were studied in 50 patients suffering nontransmural myocardial infarctions. It is concluded that

transmural myocardial infarcts tend to occur in older patients with known coronary atherosclerosis and these infarctions are frequently preceded by a period of unstable angina. The clinical course is often complicated with congestive heart failure and other major management problems. Three different groups of electrocardiographic changes were noted and all four in-hospital deaths showed the same pattern of electrocardiographic changes. The prognosis of patients suffering nontransmural myocardial infarctions is not good as evidenced by a death rate similar to reported patients suffering transmural myocardial infarction and a significant incidence of cardiovascular disability in those who survive.

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## Mexiletine in the treatment of refractory ventricular arrhythmias A report of five cases

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Ventricular premature beats (VPBs) are the most common form of ventricular arrhythmia. Because VPBs are often harbingers of more serious arrhythmias, patients who are symptomatic from the VPBs and have underlying heart disease should have treatment initiated to correct the precipitating cause and/or suppress the VPBs. To date, initiation of antiarrhythmic therapy in the asymptomatic patient who has no evidence of heart disease is controversial.

The intravenous agent that has proved to be most effective in the management of VPBs is lidocaine. But it is often necessary to manage these VPBs on a chronic basis with oral medications. There are several medications commercially available for this purpose. Unfortunately, many patients cannot tolerate these drugs or the agents are ineffective, even in combination therapy in achieving adequate control. Therefore, it is essential that other oral agents be developed for use in patients with chronic VPBs. A congener of lidocaine that can be given orally, mexiletine, is currently being investigated in the United States. We have successfully utilized mexiletine to control chronic VPBs in the five patients described below.

### Case reports

**Patient 1** L.C., a 59-year-old Caucasian male, was admitted to a local hospital after complaints of dizziness and palpitations. Upon arrival, he had a syncopal episode and was noted to have ventricular fibrillation (VF) which responded to DC countershock and CPR. The patient had four to five of these dizzy episodes in the few days prior to admission. During the hospitalization, it was noted that the patient had multifocal VPBs, recurrent ventricular tachycardia, and Mobitz Type I second degree AV block. Cardiomegaly was noted on chest roentgenogram and echocardiogram, but the echo did not demonstrate any left ventricular hypertrophy. Cardiac catheterization demonstrated a diffusely hypokinetic left ventricle and normal coronary arteries. Therefore, the diagnosis of primary myocardial disease was made. The recurrent ventricular tachycardia was controlled with intravenous lidocaine. The arrhythmias had been unsuccessfully controlled with therapeutic doses and combinations of quinidine 400 mg every 6 hours, procainamide 750 mg every four hours, disopyramide 150 mg every four hours, propranolol 60 mg every four hours, phenytoin 250 mg twice a day, and digoxin 250 mcg every day. Overdrive electrical pacing was also attempted without success. A permanent epicardial pacemaker was implanted as the patient had an intrinsic ventricular rate of 44/minute without drug therapy.

He was transferred to the University of Nebraska Medical Center to attempt control of his

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arrhythmia with mexiletine. Mexiletine therapy was initiated with 100 mg every six hours and was subsequently increased to 400 mg every six hours due to inadequate arrhythmia control at the lower doses. The maximum daily dosage recommended by the company is 1200 mg; thus this dosage exceeds the current recommendations. A repeat 24 hour Holter monitor at this time showed only 1 to 3 VPBs for the 24 hour recording period. It was decided that his arrhythmia was well controlled and he was discharged.

Since this time he has returned to work. An episode of ventricular tachycardia was noted which was quickly converted with an intravenous bolus of lidocaine and the mexiletine dosage was increased to 500 mg every six hours. At the next clinic visit he was noted to have some signs suggestive of toxicity: disorientation and slurred speech; therefore his dosage was decreased to 400 mg every six hours and propranolol 20 mg every six hours was added to his regimen. The patient's arrhythmia has been under control for the six months that he has been on the combination regimen. With the exception of the manifestations of toxicity noted earlier, the only adverse effect noted by this patient has been gastrointestinal irritation. This has been relatively well controlled with the concomitant administration of milk and small amounts of food taken with each mexiletine dose.

**Patient 2.** D.F., a 26 year old Caucasian male, has had syncope episodes with temporary vision loss since April 1977. Cardiac examination was normal. A 24 hour Holter monitor was performed which showed 5840 VPBs and recurrent episodes of ventricular tachycardia during the recording period. A treadmill exercise test demonstrated an increase in VPBs with exercise. Cardiac catheterization was performed which revealed mild mitral valve prolapse, hyperkinetic left ventricle and normal coronary arteries with no obstruction. Intravenous lidocaine caused suppression of both the VPBs and ventricular tachycardia. Quinidine 200 mg four times a day was initiated but had to be discontinued due to an acute elevation of his liver enzymes. Therefore his antiarrhythmic regimen consisted of the following: drugs in therapeutic doses and combinations: phenytoin 400 mg three times a day, procainamide 500 mg four times a day, digoxin 250 mcg daily, propranolol 40 mg four times daily and disopyramide 150 mg

three times a day. Propranolol controlled the ventricular tachycardia but not the VPBs and disopyramide was only able to somewhat suppress the VPBs. Mexiletine therapy was initiated at a dosage of 200 mg every eight hours and was increased to 300 mg every eight hours due to inadequate control. Arrhythmia control was documented by a treadmill exercise test and repeat 24 hour Holter monitor. On followup a few VPBs were noted and propranolol 20 mg every eight hours was added. This combination therapy caused complete suppression of the VPBs and ventricular tachycardia. He has been on this regimen for nine months with no recurrent problems. The only adverse effect has been gastric burning following each dose of mexiletine but this has been overcome by eating fruit at the time the drug was taken.

**Patient 3.** E.S., a 65 year old Caucasian female, was admitted for control of her VPBs. Her past medical history was positive for aneurysms, mild hypertension and congestive heart failure but these were well controlled with medications at this time. A 12 lead electrocardiogram did not reveal any acute changes—only non-specific ST-T changes. Physical examination revealed a fourth heart sound but no elevation of jugular venous pulses or evidence of left ventricular hypertrophy. A 24 hour Holter monitor demonstrated 11520 VPBs in the 24 hour recording period. Echocardiography did not demonstrate any left ventricular dysfunction or valvular disease to which the VPBs could be associated. Her arrhythmia did not respond to therapeutic doses of procainamide 500 mg every six hours and only partially responded to propranolol 40 mg four times a day, quinidine 324 mg twice a day and disopyramide 100 mg three times a day and lidocaine 4 mg/minute. Mexiletine 200 mg every eight hours was initiated with subsequent titration of the dosage to 300 mg every six hours. After 48 hours on this regimen a repeat 24 hour Holter monitor was obtained which demonstrated less than 1100 VPBs in the monitoring period which was considered to be a satisfactory response.

On followup the patient noted occasional dizziness and lightheadedness. This was thought to be due to the mexiletine and the dose was decreased to 300 mg every eight hours with resolution of this problem. Followup at the three

month interval demonstrated adequate control of the arrhythmia as no VPBs were noted on the 12 lead ECG or by the patient. She had a syncope episode one week prior to the three month evaluation and was hospitalized in her home town. The etiology of the syncope episode was not determined. She has been maintained on the current regimen for 3 months with no further syncope episodes or side effects.

**Patient 4 I M** ■ 53 year old Caucasian male had a positive history for hypertension and angina pectoris. His hypertension was well controlled with hydrochlorothiazide and angina pectoris was controlled with propranolol. Electrocardiographic examination revealed an old anterolateral infarction and left ventricular hypertrophy. A treadmill exercise test caused him to have ventricular bigeminy. A 24 hour ambulatory electrocardiogram revealed multifocal VPBs 43/200 by computer count. Control of the arrhythmia was attempted with quinidine 200 mg every eight hours and propranolol 40 mg four times a day but was not successful. Mexiletine therapy 200 mg every eight hours was initiated. The patient was placed on a treadmill after 48 hours of mexiletine therapy with only an occasional atrial premature contraction noted. On the three month and six month follow ups no VPBs were noted on a 12 lead ECG and the patient had not noted any extra beats. The patient has not noticed any adverse effects and has resumed some of his previous farm work.

**Patient 5 K G** ■ 50 year old Caucasian male had experienced an anteroapical myocardial infarction six months prior to this hospitalization. In the interim control of the VPBs and recurrent ventricular tachycardia was attempted with propranolol 40 mg every six hours in divided doses. Ventricular tachycardia was controlled with propranolol but not the VPBs. Mexiletine therapy was initiated at a dosage of 200 mg every eight hours with subsequent control of the arrhythmia. At the one month evaluation VPBs were noted by the patient and on a 12 lead electrocardiogram. The mexiletine dose was increased to 300 mg every eight hours. Follow up at four months showed the arrhythmia to be well controlled by ECG analysis and by the patient's subjective findings with no adverse effects noted. Recently while riding his exercise bicycle he suddenly died. Because the incident was unwit-

nessed the exact cause of death was not determined. It was suspected to be due to ventricular fibrillation that may or may not have been secondary to another myocardial infarction.

## Discussion

Mexiletine is an antiarrhythmic agent belonging to the Group II class. It is structurally related to lidocaine and possesses antiarrhythmic action analogous to lidocaine and phenytoin.<sup>1</sup> It appears that its potency on isolated tissues is between that of phenytoin and lidocaine.<sup>1</sup> Prescott and co-workers have demonstrated that approximately 88% of a dose of mexiletine is absorbed into the systemic circulation. The drug is widely distributed in the body volume of distribution approximating 9.47 L/Kg and obeys a three compartment pharmacokinetic model. Elimination is primarily by liver metabolism with approximately 8% eliminated in the urine as unchanged drug with renal elimination being dependent upon the pH of the urine.<sup>1</sup> With alkalization there is a decreased elimination of the drug but this does not appear to be clinically significant with normal urine pH.<sup>1</sup>

The dosage range commonly employed is 200 to 400 mg every eight hours.<sup>4</sup> With the exception of patient No. 1 all the patients reported here have been maintained in this dosage range. With the exception of patient No. 2 all of the patients have had satisfactory arrhythmia control with only mexiletine. The mexiletine dosage in patient No. 1 had to be decreased to control the symptoms of toxicity. At this time propranolol was added for control of his arrhythmias.

The side effects attributed most frequently to mexiletine are tremor, nausea, dyspepsia and dizziness.<sup>4,7</sup> On long term follow up Campbell and colleagues noted that 54% of their patients had adverse effects secondary to mexiletine with 31% being classified as severe. This group noted that the severity of adverse reactions increased with increasing plasma mexiletine concentrations. The gastrointestinal side effects appear not to be related to drug concentration. This is evidenced by the work of others<sup>8</sup> and by patients No. 1 and 2 in our series. These patients had some gastrointestinal discomfort soon after the mexiletine was initiated and this continued throughout therapy as the dosage was increased. Patient No. 3 had occasional dizziness and lightheadedness.

Table 1

Patient number	Daily dose (mg)	Plasma concentration (mcg/ml)
1	1600 mg	258
3	1200 mg	10
4	600 mg	0.97
5	600 mg	12

that became apparent only after intensive questioning. Her dosage was decreased with alleviation of these effects. Throughout the follow-up period on these patients 8 to 12 months no abnormalities have been noted on repeated laboratory examinations for any patient.

The therapeutic plasma concentration range for optimal suppression of ventricular arrhythmias by mexiletine is 0.5 to 2 mcg/ml.<sup>10</sup> At the time the patients were started on mexiletine therapy, we did not have a functioning assay procedure for mexiletine. Our dosing regimens were determined by the clinical response of the patients and by the occurrence of any adverse effects. In a retrospective fashion we have determined the plasma concentrations on four of the five patients. Blood was obtained by venipuncture and was centrifuged. The plasma was then stored in a frozen state. The plasma concentrations were determined by the method of Kelly<sup>10</sup> with modifications for use in our laboratory. All levels reflect the minimum plasma concentration at steady state (see Table 1). As can be readily seen all of these plasma concentrations with the exception of patient No 1 were within the therapeutic range. From the patient descriptions it can be readily seen that the arrhythmias were well controlled with these plasma concentrations. The arrhythmias were not satisfactorily controlled with mexiletine alone in patient No 2 and this necessitated the addition of propranolol to his therapy. The arrhythmias of patient No 1 were controlled with mexiletine only but due to the reduction in dosage for control of his side effects it was decided to add propranolol to his regimen. Inadequate arrhythmia control in patient No 2 may have been due to plasma mexiletine concentrations below the therapeutic range. This is

doubtful because it has been demonstrated that mexiletine dosages of 300 mg every eight hours provide therapeutic plasma concentrations.<sup>10</sup> It definitely was not the case in patient No 1 as his plasma mexiletine concentration was above the therapeutic range (see Table 1).

## Conclusion

From the preliminary data on five patients it appears that mexiletine is a potentially useful antiarrhythmic agent. Because we were able to control ventricular arrhythmias refractory to therapeutic doses of conventional antiarrhythmic therapy the potential for the use of this agent is increased. As no severe adverse effects were noted that necessitated withdrawal of this agent it appears quite safe. It is realized that the patient population is small but the success noted with mexiletine is very suggestive of the potential benefit of this medication. Only through further use of this agent will the total benefits be realized.

We would like to thank Boehringer Ingelheim Ltd. for providing us with the mexiletine capsules.

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## Atrial standstill, myocarditis and destruction of cardiac conduction system Clinicopathologic correlation in a dog

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Atrial standstill is a condition in which the atria as observed electrocardiographically and cineangiographically do not function. P waves are not observed in any lead of the electrocardiogram (ECG) and an atrial electrogram cannot be recorded from an electrode either in contact with the atria or placed within the atrial chambers. The atria cannot be paced through the electrodes in contact with it. A slow regular ventricular rhythm is observed which is either AV junctional or ventricular in origin.

Three forms of atrial standstill are recognized: (1) temporary atrial standstill is seen with sinus bradycardia, digitalis toxicity, quinine toxicity, carbon dioxide poisoning, hyperkalemia, and during or after open heart surgery; (2) terminal atrial standstill is observed with terminal sinus arrest following myocardial infarction—atrial

activity ceases prior to ventricular arrest and death; and (3) permanent atrial standstill is an irreversible condition which is associated with extensive atrial disease.

Permanent atrial standstill is a rare condition in humans. Two cases of fascioscapulothoracic muscular dystrophy have been observed to have permanent atrial standstill. In another family with myocardial disease, one member had amyloid infiltration in the right atrial appendage which was interpreted as the cause of permanent atrial standstill.

Permanent atrial standstill has not been described in a dog although temporary atrial standstill has been observed in dogs with hyperkalemia. This report describes the clinical, electrocardiographic, radiographic and pathologic features of atrial standstill in a dog.

### Case report

A 10 month old female Springer spaniel weighing 18 kilograms with a history of ascites of unknown origin was referred to the Veterinary Teaching Hospital at the University of Minnesota. Two months prior to presentation the patient had pancreatitis which responded to therapy. The owner had not observed any exercise intolerance or syncope attacks in the dog.

Physical examination revealed a slightly thin dog of normal stature. She was alert and active. The mucous membranes were pink. Femoral pulse was strong and regular. Both the pulse and heart rate were 62/minute. Heart and lung sounds were normal but no jugular pulse was observed. Abdominal organs could not be

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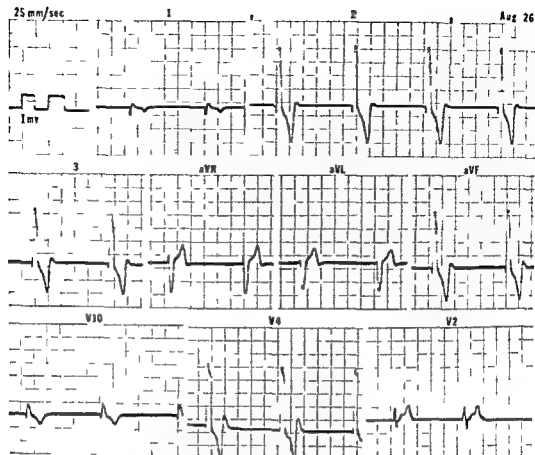


Fig 1 Standard ECG recorded from a dog with atrial standstill. A P wave is not observed in any lead and a regular idioventricular rhythm with beats/minute is noted.

palpated because of ascites. A complete blood count and urinalysis were normal. Serum potassium concentration was high normal (4.9 mEq/L) but the ratio of potassium to sodium (1.308) was normal. Serum globulin concentration was low normal (2.2 Gm/dl) while the serum albumin concentration was normal. Abdominal paracentesis showed the peritoneal fluid to be a modified transudate. Cardiomegaly with slight enlargement of the pulmonary vessels was observed on thoracic radiographs. There was no evidence of pulmonary edema.

P waves were not observed in any lead of the initial electrocardiogram (Fig 1). The ventricular rate was 60/minute and the rhythm was regular. The RR interval was 1.16 seconds and the QRS complex was 0.10 sec in duration, 0.04 sec beyond normal limits. The R wave amplitude was 4.6 millivolts. The mean electrical axis was 91 degrees in the frontal plane. The ECG was interpreted as atrial standstill characterized by bradycardia and a regular ventricular rhythm.

No increase in heart rate was observed following intravenous (IV) administration of 1.0 mg of atropine sulphate (Fig 2). Administration of an IV bolus of 0.01 mg of isoproterenol hydrochloride\* caused an increase in ventricular rate but still no atrial activity was observed (Fig 3). Pacemaker activity shifted from the original ventricular site to at least three other pacemaker foci. Within 75 seconds the rhythm and the pacemaker activity returned to the original rhythm and pacemaker site. The same response was observed subsequent to a second IV bolus injection of 0.01 mg isoproterenol hydrochloride.

During anesthetic induction for cardiac catheterization and intra atrial recording the patient developed a severe arrhythmia with multifocal ventricular pacemaker sites. Because of the risk the study was aborted and the patient was allowed to recover from anesthesia. The patient

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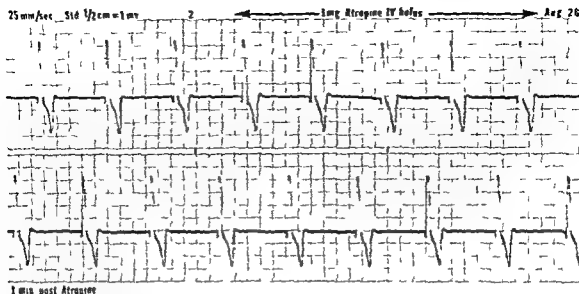


Fig 2 Lead II recorded during intravenous injection of 10 mg atropine. No change in rate or rhythm was observed one minute after completion of the injection.

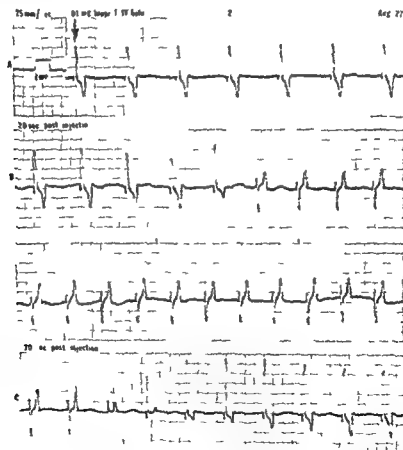


Fig 3 Lead II recorded during intravenous injection of 0.01 mg of isoproterenol hydrochloride (arrow). Pacemaker activity shifted from original locus and returned to its original site after 70 seconds. The pacemaker site shifted at least three times.



Fig 4 A P wave is not observed in any lead. Idioventricular rhythm with shifting of the pacemaker locus is observed in Leads II and aV<sub>P</sub>. A premature ventricular contraction is observed in Lead II (arrow).



Fig 5 A and B Gross cardiac specimen. A: Marked right ventricular dilatation and mottling of myocardium. B: Left ventricular hypertrophy and mild chamber dilatation.

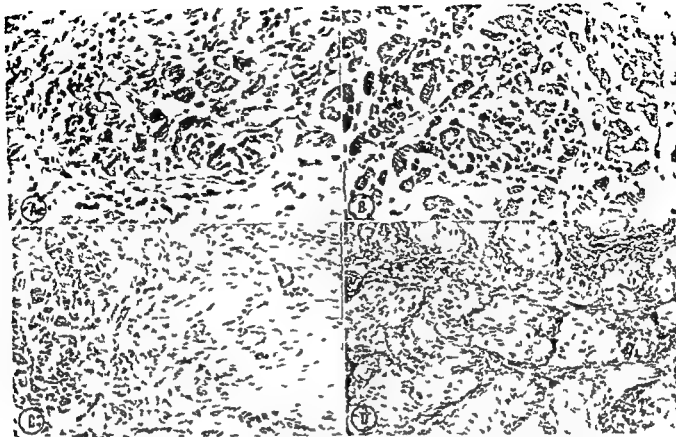


Fig 6 A through D Chronic active myocarditis. A and B Active lesions of left ventricular free wall (A) and ventricular septum (B) showing extensive lymphocytic infiltrates and focal necrosis of individual myocardial cells (Both hematoxylin and eosin original magnification  $\times 280$ ). C Healing lesion of right ventricular free wall, showing lymphocytic infiltrate and ingrowth of fibroblasts (Hematoxylin and eosin original magnification  $\times 140$ ). D Healed lesion of right atrium showing patchy interstitial fibrosis (Hematoxylin and eosin original magnification  $\times 70$ )

was discharged on 50 mg of furosemide† per day and low salt diet.

Re-examination five weeks later showed that the patient had gained 1 kilogram in weight and the degree of ascites was less marked. Pulse and heart rate were 48/minute. A Grade 2/6 short systolic murmur was present and was best heard at the third right intercostal space. P waves were not observed in any lead of the ECG. The site of pacemaker activity was changing quite frequently and premature ventricular contractions were noted (Fig 4). The patient's physical condition appeared unchanged but the ECG indicated that the rhythm was deteriorating. The patient died suddenly before a rescheduled cardiac catheteri-

zation and pacemaker implantation could be performed.

**Gross findings.** The heart at necropsy was enlarged due both to myocardial hypertrophy and to chamber dilatation. The cardiac mass was 145 grams. The right atrium and ventricle were markedly dilated (Fig 5a) whereas the left ventricle was only moderately dilated and the left atrium was of normal size (Fig 5b).

The myocardium of all chambers was focally mottled; the involved areas ranging from yellow-tan to gray-white. The yellow-tan foci were generally soft while the gray-white areas tended to be firm.

The tricuspid and pulmonary anuli were dilated while the left sided valves were normal. The coronary arteries were normal and no congenital anomalies were present.

†Lasix, National Laboratories Corp. Subsidiary of Amgen and Hoechst Corp. Somerville, N.J. 08856.

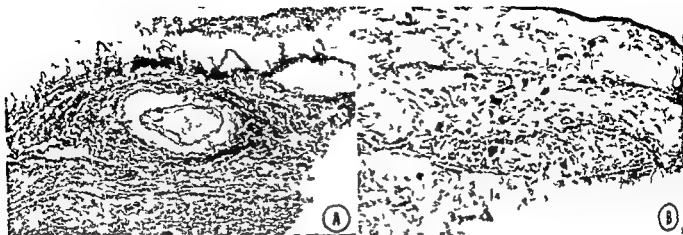


Fig 7 A and B Myocarditis involving sinus node A Normal sinus nodal artery and healed lesion showing fibrous obliteration of adjacent sinus node (Elastic van Gieson stain original magnification  $\times 70$ ) B Active lesion showing extensive lymphocytic infiltration of paranodal vagal ganglion (Hematoxylin and eosin, original magnification  $\times 140$ )

**Microscopic findings** Chronic active myocarditis was present and was extensive involving 50 to 60 per cent of each tissue section. Although these lesions individually comprised relatively small foci they often coalesced to form larger conglomerate lesions.

The foci of myocarditis varied in age ranging from active to healed lesions. In areas of active myocarditis the lesions were those of acute myocardial necrosis associated with leukocytic infiltrate (Fig 6a and 6b). The infiltrate was composed primarily of lymphocytes although neutrophils were frequently present and plasma cells were occasionally encountered. Areas of healing myocarditis were characterized by infiltrates of macrophages and lymphocytes neovascularization and ingrowth of fibroblasts (Fig 6c). Foci of healed myocarditis were represented by vascular collagen scars (Fig 6d).

The cardiac conduction system was also extensively involved by the destructive myocardial lesions described above. Although the sinus nodal artery was normal no remnants of sinus nodal tissue were identified. The region of the sinus node was replaced by either dense collagen or fibroadipose tissue (Fig 7a). Paranodal vagal ganglia were often edematous and involved with a lymphocytic infiltrate (Fig 7b).

Fascicles of atrial myocardial cells adjacent to the sinus node and to the AV node were often acutely necrotic. These fiber tracts probably represented the proximal and distal portions of the so called internodal tracts.

The AV nodal artery was normal. However the

AV node and AV bundle were involved by healed myocarditis and were totally replaced by fibrovascular adipose tissue (Fig 8a and 8b). The proximal one third of the left bundle branch was also involved by focal replacement by adipose tissue (Fig 8c). Microfocal areas of acute necrosis were present at all levels of the left bundle branch. The right bundle branch was not included in the planes of section.

The extramural coronary arteries were normal and occasional intramural branches had medial thickening. Although numerous coronary arterial branches were surrounded by foci of active inflammation an arteritis was not present.

## Discussion

The criteria for establishing the diagnosis of atrial standstill are (1) absence of P waves on ECG (2) absence of P waves on intra atrial electrograms (3) absence of A waves on right atrial pressure recordings (4) absence of atrial mobility as observed by fluoroscopy (5) inability to electrically stimulate the atria and (6) presence of regular ventricular rhythm.<sup>1</sup> Our patient had absence of P waves in all ECG leads and had a regular ventricular rhythm. Since intratrial electrogram and pressures were not recorded the possibility of a retrograde P wave in the QRS complex or T wave and atrial contraction cannot be excluded. Vagolysis with atropine had no observable effect on the ECG indicating that sinus inhibition by autonomic factors was not responsible for sinus arrest. Permanent failure of the sinus node was excluded as a sole cause

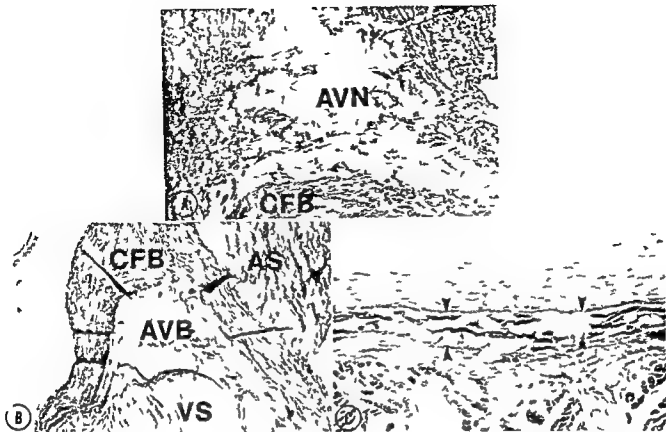


Fig 1 A through C Myocarditis involving atrioventricular conduction system A and B Healed lesions of anticipated sites of AV node (A) and AV bundle (B) showing total replacement by fibroadipose tissue (Both Elastic van Gieson stain original magnification  $\times 28$ ) C Healed lesion of left bundle branch (arrow) showing focal partial replacement by adipose tissue (Hematoxylin and eosin original magnification  $\times 70$ ) AS = atrial septum AVB = AV bundle AVN = AV node CFB = central fibrous body VS = ventricular septum

because there was no electrocardiographic evidence of other supraventricular sites of pacemaker activity nor was retrograde activation of the atria observed. The fact that the QRS complex was 0.04 sec longer than normal suggested that the pacemaker locus was of bundle branch origin rather than from the AV junctional tissue. Because of the orientation of the mean electrical axis a right bundle locus was most probable. Although absence of P waves on the ECG is also seen in sinoventricular (SV) conduction secondary to hyperkalemia we excluded the probability of SV conduction in our patient on the basis of the normal serum potassium-sodium ratio. The possible presence of isoelectric P waves or atrial fibrillation of high frequency and low amplitude cannot be absolutely excluded; however, absence of P waves in all ECG leads, and in all recordings the regular RR interval and the slow heart rate would tend to rule this out.

After administration of isoproterenol hydrochloride the pacemaker site changed from its original locus. This is probably an effect of the drug since pacemaker activity soon returned to its original site. Isoproterenol hydrochloride increased ventricular rate but did not restore atrial activity because the atria were extensively diseased and refractory to stimuli. In contrast to atrial quiescence after open heart surgery, isoproterenol hydrochloride restores normal atrial activity by hyperpolarization of the resting membrane potential.

In this case the clinical findings correlated exceptionally well with the pathologic findings. The patient had an extensive chronic active myocarditis. The sinus node was obliterated by fibrous tissue and paranodal vagal ganglia had lymphocytic infiltrates. The AV node and AV bundle were totally replaced by fibroadipose tissue and the proximal third of the left bundle

branch was partially destroyed. Atrial myocardium was extensively scarred and had multiple areas of recent necrosis. Permanent atrial standstill was therefore associated with widespread lesions of the atria and the cardiac conduction system, and the functional pacemaker probably originated in the ventricles.

The finding common to all cases of permanent atrial standstill appears to be pathologic involvement of the atria. It has been observed that endocardial fibrosis and myocardial infarction will raise the stimulation threshold for myocardium, thus partially explaining why the diseased atrium is refractory to internal and external stimuli.<sup>1</sup>

### Summary

A case of permanent atrial standstill is described in a 10-month-old dog with ascites as a presenting complaint. The patient had absence of P waves in all leads in numerous ECGs and had a regular idioventricular rhythm. Pathologically, the patient had multiple areas of atrial and ventricular myocardial necrosis and fibrosis with chronic active myocarditis and obliteration of the SA and AV node and AV bundle.

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## Depression of intramyocardial oxyhemoglobin dissociation by angiographic contrast media

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Several potentially deleterious effects of contrast material have been described in the past decade.<sup>1-4</sup> These have included effects of the injection of a hyperviscous and hypertonic solution on the size and shape of red cells, certain hemodynamic and electrocardiographic changes, a tendency to acidosis, and a depression of blood calcium levels. The production of acidosis by the injection of water-soluble contrast materials has been clearly demonstrated.

However, the significance of this finding upon oxygen delivery by red blood cells has been questioned. When oxygen delivery is described in terms of P50, that value is expressed either as P50 at pH 7.4 or P50 *in vivo*. Usually plasma pH adequately reflects the intra-red blood cell pH throughout the physiologic range. However, angiographic contrast medium has been shown to alter the red blood cell pH gradient. Therefore, in this situation, plasma does not reflect intra-red blood cell pH. Previous workers have measured intra-red blood cell pH after the addition of contrast medium with differing results.

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The purpose of this study was to examine the effects of contrast medium in an experimental system where extracellular pH was kept constant using a highly buffered red blood cell solution. Thus, all P50s were measured under the same conditions (pH 7.4, PCO<sub>2</sub> 40, and temperature 37°C), and any changes seen would therefore directly reflect changes in intra-red blood cell pH. In addition, the effect of contrast medium on the red cell pH gradient was examined anaerobically. It has previously been shown that contrast media do not alter red blood cell 2,3-DPG,<sup>5</sup> which is the only other known explanation for acute changes in P50 in this system.

In addition to the *in vitro* studies, *in vivo* studies were performed on blood drawn simultaneously from the coronary sinus and peripheral arterial system prior to and one minute and five minutes after selective injection of the left coronary artery with contrast material.

### Methods

**In vitro studies.** Blood was drawn from the antecubital vein of normal volunteers into tubes containing sodium heparin. Methylglucamine 3.5 diacetamide 2.4-truodobenzoate 66% aqueous solution (Renografin 76) was added to blood in concentrations varying from 0.2 to 0.8 c/c blood and incubated for a constant time interval prior to measurement of P50. The effect of variation of incubation time from one minute to 30 minutes was evaluated at a Renografin concentration of 0.6 c/c blood.



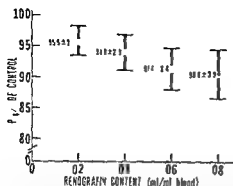


Fig 1 P<sub>50</sub> after incubation with Renografin at various concentrations as shown. All samples were incubated at a constant time interval of 30 minutes. Results are expressed as percentage of control values (without Renografin)

Table 1 Red blood cell pH gradients (Plasma pH-Intracellular pH) in the control state and after 30 minutes of incubation with Renografin 0.6 cc/cc blood

	Control	Renografin
	0.24	0.07
	0.20	0.00
	0.20	0.08
	0.21	0.05
	0.20	0.06
	0.20	-0.03
	0.20	-0.02
Mean	0.207	0.03
Std dev	0.015	0.044
T =	11.02	
P <	0.001	

Blood hemoglobin was measured with an IL 182 cooximeter

Blood oxygen dissociation curves were obtained by a modification of the method of Longmuir and Chow. The curve was measured at PCO<sub>2</sub> 40 pH 7.4 and 37°C on whole cell suspensions in 0.16 M sodium phosphate buffer in a 30 cc closed cell. Buffers and blood samples were thoroughly equilibrated with a gas mixture containing 19.6% oxygen prior to introduction into the chamber. The cell suspensions were deoxygenated by beef heart mitochondrial succinate respiration (with out CO<sub>2</sub> production) and the P<sub>50</sub> was measured with a membrane type oxygen electrode (YSI model 53 oxygen monitor). The oxygen signal was continuously recorded on a Kip and Zonen BD 9 recorder. All curves were measured in duplicate and duplicate determinations on the same sample agreed to within  $\pm 0.25$  mm Hg.

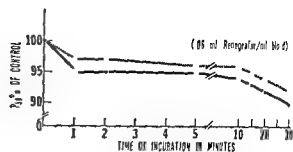


Fig 2 Effect of variation of incubation time on P<sub>50</sub> with a constant concentration of 0.06 ml Renografin/ml blood. P<sub>50</sub>s are expressed as percentage change from control (with out Renografin)

Red cell and plasma pH's were measured using an IL 213 blood gas analyzer at 37°C. The red cell lysate was obtained by the freeze thaw technique. pH gradients were therefore obtained across the red cell membrane in the control state and after incubation with Renografin for minutes (0.6 cc Renografin/cc blood) 37°C.

**In vivo studies** Eleven adult patients who were undergoing cardiac catheterization and selective coronary arteriography were studied. Arterial catheters were introduced percutaneously through the femoral artery and venous catheters via a cutdown into the basilic vein. The venous catheter was positioned in the proximal coronary sinus. The position was verified by a combination of the fluoroscopic location and by the low oxygen saturation. In eight patients studies were performed approximately ten minutes after left ventriculography. In three patients studies were performed prior to left ventriculography.

Prior to the first coronary injection control samples were obtained from the proximal coronary sinus and the central aorta. Contrast material was then selectively injected into the left coronary artery (approximately 6 to 12 ml over 4 seconds). One minute and five minutes after injection repeat blood samples were obtained from the proximal coronary sinus and the central aorta. Blood samples were cooled on ice at oxygen hemoglobin dissociation curves and P<sub>50</sub> were determined in duplicate within twelve hours.

## Results

**Effect of Renografin on blood P<sub>50</sub> in vitro** The effects of Renografin on whole blood P<sub>50</sub> at concentrations (as outlined above) which would be attained during cardiac catheterization were studied on blood samples drawn from eight

Table II Differences in P50 between coronary sinus and aorta before and after left coronary arteriography

Control			1 Minute			5 Minute		
CS	Ao	$\Delta$ (CS Ao)	CS	Ao	$\Delta$ (CS Ao)	CS	Ao	$\Delta$ (CS Ao)
29.86	—	—	28.46	29.71	-1.25	29.08	29.71	-0.63
29.08	28.58	-0.50	26.77	29.23	-2.46	26.28	28.25	-1.97
26.63	26.62	0.01	26.92	—	—	26.91	27.19	-0.28
27.43	28.53	-1.10	28.84	30.40	-1.56	26.19	27.12	-0.93
26.11	26.28	-0.17	25.77	26.44	-0.67	26.27	26.61	-0.34
25.56	25.56	0	22.56	22.83	-0.27	23.11	23.11	0
25.78	25.78	0	25.30	25.90	-0.60	25.23	25.51	-0.28
28.93	28.57	-0.36	28.57	28.21	0.36	29.11	29.11	0
27.30 ±	27.13 ±	-0.20 ±	26.52 ±	27.67 ±	-1.06 ±	26.52 ±	27.07 ±	-0.55 ±
1.86	1.37	0.49	2.19	2.58	-0.39	1.96	1.10	0.86
SEM .50	SEM .52	SEM .18	SEM .75	SEM .57	SEM .36	SEM .69	SEM .74	SEM .23

Significant  $p < 0.01$ Abbreviations: CS = coronary sinus; Ao = aorta;  $\Delta$  = difference of aorta from coronary sinus; SEM = standard error of the mean.

patients. For this series of experiments all blood samples were incubated with Renografin at a constant time interval of 30 minutes. The average blood Renografin concentration attained during angiography was estimated at 0.2 to 0.4 cc Renografin/cc blood. This is based on an average total dose of 100 to 200 cc of contrast at an average blood volume of 5 liters. Concentration added *in vitro* ranged from 0.2 to 0.8 cc Renografin/cc blood in all eight patients. The results are depicted in Fig. 1 as percentage decrease at each concentration when compared to the control  $P_{50}$ . As shown in Fig. 1 the  $P_{50}$  progressively decreased throughout the range of concentrations studied. In two patients in whom higher concentrations were studied,  $P_{50}$  decreased even further. The changes from control values were significant ( $p < 0.1$ ) by Student's *t* test for Renografin concentration up to 0.8 ml/cc blood.

The effect of the time of incubation of Renografin with blood on  $P_{50}$  was studied at a dose of 0.6 cc Renografin/cc blood. The time of incubation refers to the time interval prior to introduction of the blood sample into the closed cell. Results of variation of incubation time are shown in Fig. 2. In both patients studied a significant decrease in  $P_{50}$  was seen at one minute incubation. This remained constant up to ten minutes of incubation beyond which point there were further decreases at 15, 20, and 30 minutes of incubation. Although the absolute decrease at one minute was only 3 to 5% of the control value this represented a change of 7 mm Hg which

is well beyond our range of reproducibility on the same blood sample (i.e.  $\pm 0.2$  mm Hg).

The effects of Renografin 0.6 cc/cc blood on the red blood cell transmembrane pH gradient were studied *in vitro* in seven normal subjects. The differences between plasma and intracellular pH were compared in the control state and after 30 minutes of incubation with Renografin. The addition of Renografin decreased the plasma pH and the difference between plasma and intracellular pH (Table I). The mean pH gradient was  $0.21 \pm 0.01$  prior to the addition of Renografin. The gradient after incubation with Renografin was  $0.4 \pm 0.4$ ,  $p < 0.001$ .

**In vivo effects of Renografin.** Control samples were simultaneously obtained from the proximal coronary sinus and central aorta and repeat samples were obtained at one minute and five minutes following injection of the left coronary artery in the 11 patients studied. In eight patients these determinations were performed after left ventriculography and in three they were performed prior to left ventriculography. The results in the initial group of eight patients are shown in Table II. There is no significant difference between  $P_{50}$ s from coronary sinus or aorta in the control period. At one minute after left coronary injection the decrease of coronary sinus as compared to aortic  $P_{50}$  is significant ( $p < 0.1$  Student's *t* test). This difference is reduced by five minutes post injection when values approach the control state.

When the coronary arteries were injected prior to left ventriculography there was no difference between simultaneous coronary sinus or aortic samples prior to injection or one minute or five minutes after injection

## Discussion

Intravascular injection of radiographic contrast material results in a complex series of potentially deleterious effects. Most of these effects have been attributed to the contrast material's hypertonicity and high viscosity. A lowering of ionized calcium levels has been described secondary to angiographic contrast material which may be implicated in cases of hypotension secondary to contrast injection.<sup>8</sup>

Initially, the acidosis secondary to contrast material was thought to affect oxyhemoglobin dissociation,<sup>9</sup> but recently it has been stated that there is no effect on oxyhemoglobin dissociation since intra red blood cell pH is not affected by angiographic contrast media. Instead it was stated contrast causes an extrusion of hydrogen ions from the red cell.<sup>10</sup>

The results of this study are in agreement with that of Lichtman and associates<sup>11</sup> referred to above. The decreased  $P_{50}$  seen in our *in vitro* and *in vivo* studies secondary to contrast material is explained as follows. The contrast medium (Renografin 76) is a salt of an impenetrable anion and by balancing negative ions within the red cell alters the transmembrane ionic charge gradient (see Table I). When the red cell interior is strongly buffered with respect to the suspending medium, the result is a relative acidification of the medium without change in intracellular pH, when the suspending medium is strongly buffered as in our studies the reduction of the pH gradient will result in an increase in intracellular pH. The  $P_{50}$  of the blood then decreases due to the Bohr effect<sup>12</sup> when compared to the same blood  $P_{50}$  prior to addition of contrast medium with an intra red blood cell pH of 7.2. We and others have shown that this effect is both dosage and time dependent.

The exact situation *in vivo* is not known and is probably dependent upon blood flow and relative buffering capacity of intra and extra red blood cell spaces. The equilibrium studies of Lichtman and associates are at one extreme where the entire pH change is extracellular. The red blood cell suspension system that we have examined is

at the other extreme where the entire change is intracellular. The actual situation *in vivo* would depend on the relative buffering capacity of intra and extra red blood cell spaces.

In areas of rapid blood flow the changes described are of little consequence since the dye is rapidly diluted. However in areas of myocardium distal to a critical coronary lesion these effects may take on more significance. This is theoretically possible for two reasons. First, the stagnation of blood flow would allow tissues to be exposed to the effects of the contrast media for a longer time period. Second, the chronically ischemic tissue bed experiences a shift to anaerobic metabolism with an increase in glucose consumption, lactate production, a decrease in pH and ion shifts.<sup>13,14</sup> If ischemia is severe enough there may be a release of cardiac lysosomal enzymes<sup>15</sup> which may impair transport functions of cell membranes. This would lessen the metabolic differences between intracellular and extracellular spaces. The increased total CO<sub>2</sub> produced by ischemia<sup>16</sup> would offer a better buffering capacity than normal tissue at normal rates of blood flow. These conditions would favor the kind of changes in  $P_{50}$  seen in our study done in a highly buffered red blood cell solution. The magnitude of these effects *in vivo* is unknown. In this regard Calfield and colleagues<sup>17</sup> using a protocol similar to ours found that the effect of Renografin on ionized calcium was of a greater magnitude and duration in patients with coronary artery disease than in normals.

When the normal sequence of cardiac angiography was reversed (i.e. coronary arteriography performed prior to left ventriculography) no effect on  $P_{50}$  was detected one minute or five minutes after the injection of the left coronary artery. This suggests that the effects are additive and dose related as seen in our *in vitro* studies.

The ultimate effects of contrast medium on oxyhemoglobin dissociation are complex and dependent upon dosage and blood flow but the direction of change in  $P_{50}$  is probably most influenced by the buffering capacity of the ambient tissue.

## Summary

The effect of the addition of radiographic contrast material (Renografin) to blood on the oxyhemoglobin dissociation curve and  $P_{50}$  was measured by a metabolic deoxygenation tech-

nique in a strongly buffered red cell suspension. With incubation time constant, increasing doses produced progressive decreases in P50. With incubation time varied at a constant dose, a decrease in P50 was seen after only one minute.

In addition, in vivo studies were performed on 11 patients undergoing cardiac catheterization. Simultaneous proximal coronary sinus and aortic samples were drawn as controls and then at one minute and five minutes after injection of the left coronary artery. In eight patients studies were performed after and in three prior to left ventriculography.

At one minute after left coronary injection there was a significant decrease of coronary sinus as compared to aortic P50 ( $p < .10$ ) (only when left ventriculography was performed prior to coronary arteriography).

The magnitude of these effects in vivo is unknown but they would be expected to be more severe in areas distal to a critical coronary lesion due to stasis of blood flow and ischemic metabolic changes.

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# Primary myocardial disease Correlation with clinical findings, angiographic and biopsy diagnosis

Follow up of 139 patients

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It is customary to apply the term primary myocardial disease or cardiomyopathy to an abnormal state of the myocardium unrelated to arterial hypertension coronary atherosclerosis, syphilitic rheumatic and congenital heart disease. These terms have been used to denote an affection of unknown etiology and conditions having a specific cause. On the basis of ventricular function and pathologic findings Goodwin<sup>1</sup> has classified the cardiomyopathies into four main types: congestive hypertrophic with or without obstruction, constrictive (restrictive) and obliterative. The clinical manifestations of patients with these types of myocardial disease of known or unknown etiology may be similar. However, a variety of clinical features and hemodynamic measurements may have some correlation with prognosis. Hatle and co-workers<sup>2</sup> and Goodwin<sup>1</sup> noted a favorable course in patients with cardiac hypertrophy and in others in whom systemic hypertension developed but patients with low voltage (ECG), left atrial enlargement, high filling pressure, low cardiac output and elevated pulmonary arterial resistance seemed to have unfavorable clinical courses. Feil and

colleagues<sup>3</sup> found a high survival rate in groups of patients with a mass/volume ratio greater than 0.90 and ejection fraction greater than 0.50 suggesting hypertrophy was an important compensatory mechanism. According to Demakis and co-workers<sup>4</sup> the long term prognosis of patients with congestive heart failure is related to the time required for the heart to return to normal size following conventional therapy. Shugoll and associates<sup>5</sup> found that there was no relationship between the size of the heart and survival.

In this study we have attempted to correlate various clinical manifestations of patients with primary myocardial disease, compare the course of patients with congestive and noncongestive cardiomyopathies and assess the prognostic value of myocardial biopsy.

## Materials and methods

One hundred fifty nine patients were selected for this study. The criteria for selection were a myocardial biopsy and an angiographic diagnosis of primary myocardial disease. There was no evidence of congenital rheumatic syphilitic heart disease or obstruction of the coronary artery circulation greater than 50%. The term primary myocardial disease applies to the idiopathic group and those with specific etiology as suggested by Segal and colleagues.<sup>6</sup> The biopsy technique was described in 1972.<sup>7</sup> To avoid a possible error in diagnosis 16 patients with systemic blood pressures of 150/100 mm Hg and above were

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excluded. Although the diastolic blood pressure may be temporarily elevated in patients with primary myocardial disease and congestive failure the findings are similar in hypertensive cardiovascular disease.<sup>1-4</sup> One patient who died one day after a myocardial biopsy was excluded. Of the remaining 142 patients three were lost to follow up (97.8% follow up).

### Clinical features

The history and physical findings elicited days to several weeks prior to cardiac catheterization and angiographic studies were reviewed. A history of congestive heart failure or a cardiac arrhythmia may be inaccurate; therefore only abnormal clinical findings present on clinical examination were recorded.

The following manifestations were encountered:

- 1 Congestive heart failure—ventricular gallop (third heart sound) rales, hepatomegaly or peripheral edema alone or in any combination on physical examination. Noncardiac causes of rales, hepatomegaly and peripheral edema were excluded.

- 2 Cardiac arrhythmia—an arrhythmia other than sinus arrhythmia present on a standard electrocardiogram.

- 3 Angina pectoris—discomfort in the anterior chest that was precipitated by excessive physical activity or emotional stress or by both, relieved within 15 minutes by rest or nitroglycerin. Some patients had rest pain.

- 4 Chest wall pain—discomfort usually sharp and unrelated to physical or emotional stress of seconds to hours in duration.

- 5 Shortness of breath—breathlessness of short duration during activity or at rest.

- 6 Palpitation—awareness of a rapid and forceful heartbeat that was usually regular.

- 7 Fatigue—exhaustion or tiredness mostly during activity.

Eight patients had drinking patterns considered to be abnormal. Five patients drank beer only in quantities of 1.5 to 5.5 quarts daily for five to 15 years. The others reported a daily intake of the same beverage in excess of 1½ pints, seven to 26 ounces of whiskey or 26 ounces of wine daily for five to 25 years.

**Coexisting disease.** Twelve patients had diabetes mellitus. Chronic obstructive pulmonary

disease was present in one patient. The diagnoses were polyneuropathy, multiple myeloma, hypothyroidism, lupus erythematosus and rheumatoid arthritis in five patients (one patient each).

**Cardiac catheterization and angiographic diagnosis.** The diagnosis was based on analysis of pressure curves, hemodynamic findings and single plane angiograms (multiple views). The classification of Goodwin<sup>5</sup> was used.

- 1 Congestive—dilatation and generalized impairment of contractility of the left ventricle were present.

- 2 Hypertrophic with or without obstruction—size of the left ventricular cavity was normal or small with accentuated trabecular pattern and prominent papillary muscles with or without functional constriction of septal perforators in systole.

- 3 Constrictive (restrictive)—the left ventricular chamber was dilated or of normal size with unpaired contractions or reduced diastolic pulsations or both with an absent atrial kick. Most of the hemodynamic findings and the double density parallel to the cardiac border usually demonstrated by selective coronary arteriography in patients with pericardial disease were absent.

**Myocardial biopsy.** In most patients a myocardial biopsy was performed a few days following cardiac catheterization and angiographic studies. The other patients had biopsies performed two to six weeks later. The method for preparing and staining the biopsy specimens has been described.

**The light microscopic findings**

- 1 Myocardium—no pathologic diagnosis.

- 2 Myocardial hypertrophy—increase in breadth of muscle fibers by enlargement and blunting of the ends of myocardial cell nuclei with and without perinuclear vacuoles or clear zones.

- 3 Myocardial fibrosis—increase in connective tissue surrounding small arteries and arterioles and connective tissue between muscle fibers.

- 4 Cellular infiltration—presence of neutrophils, lymphocytes or plasma cells in the interstitium.

- 5 Amyloid deposition—pale, pink staining ground glass appearing interstitial deposits (hematoxylin and eosin) appear as magenta colored metachromatic material on crystal violet stained preparation.

Table 1 Clinical manifestations of 139 patients

	No of patients	Per cent
Congestive heart failure	54	38.5
Cardiac arrhythmias	40 (total)	28.7 (total)
Supraventricular	18	45.0
Ventricular	21	52.5
Complete heart block	1	2.5
Angina pectoris	28	20.1
Other symptoms	29	20.8
Asymptomatic	8	5.7

13 patients had angina pectoris only.

Shortness of breath, palpitations, chest wall pain or fatigue only.

■ Small vessel disease—walls of the vessels 70 to 150 microns in diameter showed an increase in stainable collagen (Masson stain) beneath the intima and irregularly throughout the muscle layer.

7 Basophilic degeneration—deposits of blue gray hyaline material within the myocardium (hematoxylin and eosin). The material stained intensely with PAS stain and failed to give a metachromatic reaction with crystal violet.

Management Congestive failure was treated with sodium restriction, digitalis preparations and diuretics. The duration of bed rest and limited activity depended on the response to medical management. The average period of bed rest was four to six weeks. Cardiac arrhythmias were managed with the usual antiarrhythmic drugs: digitalis preparations, quinidine sulfate and procainamide. A permanent cardiac pacemaker for conduction defects was inserted in four patients. The patients with chest pain suggestive of angina pectoris were advised to avoid precipitating factors. Rest pain was treated with mild analgesics. The same medication was prescribed for chest wall pain. Cerebral embolus or pulmonary embolus occurred in four patients. All but one received anticoagulant therapy which was discontinued in one patient because of gastrointestinal bleeding. General measures consisted of adequate rest and a well balanced diet. Fatigue and alcoholic beverages were to be avoided. A vitamin supplement was added when a nutritional factor was suspected. The two patients with hypertrophic cardiomyopathy with obstruction received propranolol in a dose of 80 mg daily. Patients with polyneuropathy and lupus erythematosus received corticosteroids. The same drug

was administered to patients with histologic findings of cellular infiltration and to two patients with severe congestive failure and uncontrolled cardiac arrhythmias. The patient with hypothyroidism was treated with thyroid medication.

Follow up Data on 139 patients were obtained from attending physicians, patients' spouses, members of the family by questionnaires and by telephone contacts. In some patients the information was recorded from the clinical and medical records and autopsy reports. From these data it was difficult to determine the duration of clinical heart disease, therefore the follow up period was the interval of time between cardiac catheterization and angiography and the last date examination data was obtained or the death of the patient. There were 99 men (mean age 47 years) and 40 women (mean age 43.3 years). The follow up of surviving patients was a minimum of 13 months and a maximum of 119 years (14 months), mean 5.4 years (65 months).

## Results

Clinical manifestations The clinical findings at the initial examination are listed in Table 1. Congestive failure was present in 48 of 111 patients (42.4%) with congestive cardiomyopathy. Five of eight patients (62.5%) with constrictive cardiomyopathy and one of 18 patients (5.5%) with hypertrophic myocardial disease had the same clinical manifestations. Of the 54 patients with congestive failure, 11 had coexisting cardiac arrhythmias. Atrial fibrillation (four patients) and premature ventricular contractions (three patients) were the most common arrhythmias. Atrial flutter (two patients) and premature atrial contractions (two patients) were the other arrhythmias.

Cardiac arrhythmia without congestive failure was present in 29 patients (20.8%). The most common arrhythmias were premature ventricular contractions and atrial fibrillation. These arrhythmias (20 patients), ventricular tachycardia (two patients) and supraventricular tachycardia (one patient) occurred in those with congestive cardiomyopathy. Both premature ventricular contractions and ventricular tachycardia occurred in two patients, ventricular tachycardia and ventricular fibrillation were present in one other patient. Premature ventricular contractions was the only arrhythmia in one patient with constrictive cardiomyopathy. Complete heart

block and ventricular tachycardia were the manifestations in two patients with hypertrophic myocardial disease

Chest pain suggestive of angina pectoris was elicited in 28 patients (20.1%). One of these had atypical angina (chest discomfort relieved by rest in 30 minutes). Angina pectoris was the only symptom in 19 of 28 patients. In these the angiographic diagnosis was congestive cardiomyopathy (15 patients) and hypertrophic cardiomyopathy (four patients).

Of 29 patients (20.8%) with shortness of breath, palpitations, chest wall pain or fatigue only 20 had congestive myopathy. The others had hypertrophic (seven patients) and constrictive cardiomyopathy (two patients).

Only eight patients (5.7%) had no symptoms. The electrocardiographic findings shown in Table II were the reasons for the investigations. In three patients a systolic murmur was present. The types of myopathy were congestive (four patients) and hypertrophic without obstruction (four patients).

**Cardiac catheterization and angiographic findings.** The diagnosis of congestive cardiomyopathy was made in 113 patients. Prolapse of the mitral valve without mitral regurgitation was noted in two patients. One of 11 patients with mitral regurgitation had prolapse of the mitral valve. In 18 patients the findings were consistent with hypertrophic cardiomyopathy. Two of these 18 patients had evidence of left ventricular outflow tract obstructions without mitral regurgitation. Constrictive cardiomyopathy was the diagnosis in eight patients.

**Myocardial biopsy.** The biopsy played a minor role in the management in most patients but it provided an opportunity to compare tissue diagnosis with other parameters. Myocardial hypertrophy or fibrosis or both was present in 43 of 54 patients (79.6%) with congestive failure. The same tissue diagnosis was made in six of the eight asymptomatic patients (75%) and in 46 of 77 symptomatic patients (59.7%) without congestive failure. Seventy-four of 113 patients (65.4%) with congestive cardiomyopathy had the same biopsy findings as did 16 of 18 patients (88.8%) and five of eight patients (62.5%) with hypertrophic and constrictive myopathy respectively. Small vessel disease was not associated with specific clinical manifestations (no angina pectoris). It was present in two of eight patients (25%) with constrictive

**Table II** Indications for study in asymptomatic patients

Abnormal findings	Type of cardiomyopathy	
	% of patients	
	Congestive	Hypertrophic
ECG changes		
LBBB	3	
RBBB		1
Infarction†	1	1
LVH		2

LBBB = left bundle branch block; RBBB = right bundle branch block; LVH = left ventricular hypertrophy.

Cardiac catheterization and angiographic diagnosis.

†Infarct related QRS abnormalities and intramural.

ive myopathy compared to two of 18 (11%) and two of 113 patients (1.8%) with hypertrophic and congestive cardiomyopathy, respectively. Shortness of breath, palpitation, chest wall pain or fatigue were the most frequent symptoms and congestive myopathy was present in most of the 35 patients (94%) with no pathologic diagnosis.

**Mortality rate.** The 5 year total mortality rate was 37.4% (52 of 139 patients). Although some of the information obtained concerning the mechanism of death may not be reliable, myocardial disease was the most likely cause in 47 of the 52 patients (cardiac mortality rate 33.8%). Cerebral vascular accident (cerebral embolism not absolutely excluded), drug overdose, self-inflicted gunshot wound and possible pulmonary embolism following pelvic surgery were considered noncardiac deaths in five patients. The minimum and maximum survival for 47 patients whose deaths were considered cardiac was two weeks and 90 months, respectively, mean 21 years (25.2 months). Thirty-five deaths were considered to be caused by congestive failure. In five of these the initial findings were chest pain, shortness of breath, palpitations or cardiac arrhythmia. A cardiac arrhythmia was the most likely cause of death in 12. Arrhythmia was suspected in ten of 11 deaths in patients without congestive failure or cardiac arrhythmias or both in the past (including one asymptomatic patient). There were four sudden deaths: two patients were found dead in bed, one collapsed in a department store and one died while running.

The survival curves shown in Fig. 1 using the life table method (Table III) demonstrate a



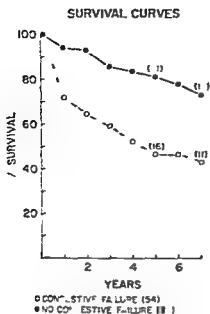


Fig 1 Survival curve for patients with and without congestive heart failure. The number of patients living at the beginning interval in parenthesis

Table III Life table

Interval followed (yr)	% of patient		
	Last report		Total no persons living at beginning of interval
	Dead	Living	
0-1	10 (3)	41	54 (60)
1-2	4 (1)	3 (1)	39 (49)
2-3	4 (0)	1 (10)	32 (44)
3-4	3 (1)	3 (20)	27 (62)
4-5	2 (1)	3 (0)	21 (41)
5-6	0 (1)	1 (1)	16 (31)
6-7	1 (1)	1 (1)	13 (18)
+	1 (1)	10 (14)	11 (15)

Interval 0-1 = 100% survival, others in parentheses

Interval 1-2 = 100% survival or dead from intercurrent disease

significant difference in survival rates in one year ( $P < 0.001$ ) and five years ( $P = 0.001$ ) in patients with and without congestive heart failure. The survival curves were based on the methods described by Cutler and Ederer. The chi square method with Yates' correction formula was used to determine the statistical significance of different mortality rates. In 54 patients with congestive failure the 5 year total mortality rate was 57.4%. There were three noncardiac deaths resulting in a five year cardiac mortality rate of 51.8%. The

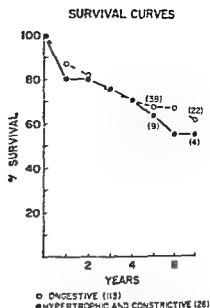


Fig 2 Survival curve for patients with congestive cardiomyopathy, the hypertrophic and constrictive types are compared. Number of patients in parenthesis

highest cardiac mortality rate was in the first year (27.7%). Four of 15 patients (26.6%) with congestive failure who died within one year had a coexisting cardiac arrhythmia (Table IV). The next highest number of cardiac deaths occurred between one and three years (eight patients). Of these two patients (25%) had congestive failure and a cardiac arrhythmia. The 5 year cardiac mortality rate of 85 patients without congestive failure was 16.4% (only one noncardiac death). Of these the highest cardiac mortality rate occurred in 29 patients (34.4%) with a history of shortness of breath, palpitation, chest wall pain or fatigue. The groups with the least 5 year mortality rate were asymptomatic (12.5%), angina pectoris only (10.5%) and cardiac arrhythmias only (3.4%).

Of the 12 patients who had diabetes mellitus seven (58%) had congestive heart failure or cardiac arrhythmias or both. There were six cardiac deaths (50%). Three of these patients had congestive failure or cardiac arrhythmias or both. Congestive heart failure was the cause of death in the one patient with hypothyroidism. The four patients with polyneuropathy, multiple myeloma, rheumatoid arthritis or lupus erythematosus had been followed for a minimum of 40 months.

The survival curves of patients with congestive cardiomyopathy and combined hypertrophy and

Table IV Relation of clinical manifestations and mortality

Presenting clinical symptom	Total no of patients	Mortality								Cardiac mortality (per cent)	Total mortality (per cent)
		Years after cardiac catheterization									
		0-1	1-2	2-3	3-4	4-5	5-6	6-7	7+		
Congestive failure	43	11	3 (3)	3	3	2		1	1	24 (55.8)	27 (62.1)
Congestive failure and arrhythmias	11	4	1	1						11 (54.5)	
Arrhythmias without failure	29	(1)			1			1	1	3 (10.3)	4 (13.8)
Angina pectoris only	19	1	1							2 (10.5)	
Other symptoms	29	4		5		1	1		(1)	11 (37.9)	12 (41.3)
Asymptomatic	8			1						1 (12.5)	
Total	139									47 (33.8)	57 (40.9)

Non cardiac deaths in parentheses

Other symptoms—dyspnea, palpitation, chest wall pain, or fatigue

constrictive cardiomyopathy are demonstrated in Fig 2. The death rate of three patients with amyloid heart disease accounts for the high mortality rate of the noncongestive myopathy group within the first year. The average annual mortality rate in the first five years for patients with congestive myopathy was 6.5% per year; the average annual attrition rate for patients with hypertrophic and constrictive myopathy was 7.2% per year. If the three patients with amyloid heart disease (constrictive type) are excluded, the average attrition rate for the first five years for the combined types (hypertrophic and restrictive) was 5.9% annually.

Patients whose biopsies showed no pathologic diagnosis survived the longest (Fig 3). Excluding the patients with amyloid heart disease, myocardial fibrosis with or without hypertrophy only was associated with the highest mortality rate (Table V). When 18 patients with myocardial hypertrophy or fibrosis or both and cellular infiltrate, small vessel disease or basophilic degeneration are included, the death rate was similar (46.6%). In contrast, the death rate was 16.6% in six patients with cellular infiltrate, small vessel disease or basophilic degeneration only. Nineteen patients were examined at autopsy. Biopsy and autopsy histologic findings in all patients are compared in Table VI. The same tissue diagnosis was present in almost one half of the patients (47.4%). In four of ten patients with a new diagnosis, the autopsy findings were absent in the biopsy and in six patients not all of the pathologic changes were present in the two groups.

## Discussion

It is difficult to determine the accuracy of the history (including drinking habits) to monitor how carefully treatment was followed or to control all the factors that could influence the course of the patient with primary myocardial disease. For example, only eight of 139 patients (5.8%) admitted the heavy use of alcohol, which is more than 50% below the general adult population studied by Cahalan and colleagues.<sup>1</sup> Although abstinence was advised, the degree of compliance is unknown. The same applies to rest and limitation of physical activity and emotional stress. The selection of medications and dosage of drugs could affect survival. The dose of propranolol (80 mg daily) in the two patients with hypertrophic cardiomyopathy with obstruction could have been ineffective (50% mortality rate). The number of patients is too small to be significant, but a recent report by Frank and associates<sup>14</sup> suggested high doses (average 340 mg daily) may be associated with a favorable prognosis. Hardarson and co-workers<sup>15</sup> found beta adrenergic blocking agents in a dose range of 20 to 240 mg daily to be disappointing but concluded a higher dosage may offer better protection from sudden death. If the limited value of history, variations in ability and experience of physicians attending the patient, and inability to measure cooperation of the patient are accepted, the correlation of various parameters with survival may be meaningful.

Congestive heart failure was associated with a high mortality rate (56%). The addition of a

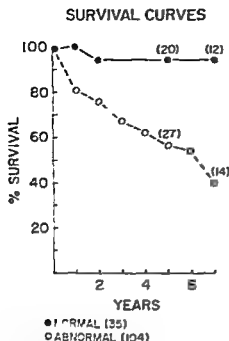


Fig 3 Survival curves for patients with normal and abnormal microscopic findings (myocardial biopsy). Number of patients in parentheses.

Table V Correlation of biopsy diagnosis with cardiac mortality

	Total no of patients	Cardiac deaths (per cent)
Myocardium, no pathologic Dx	30	5.7
Myocardial hypertrophy	20	30.0
Myocardial fibrosis	21	52.3
Myocardial hypertrophy and fibrosis	36	50.0
Cellular infiltrate	3	33.3
Amyloid	3	100.0
Small vessel disease	1	0
Basophilic degeneration	2	0
Myocardial hypertrophy and fibrosis with CI, SVD or BAS	18	33.3

Abbreviation: CI = cellular infiltrate; SVD = small vessel disease; BAS = basophilic degeneration.

cardiac arrhythmia seemed to have no major influence on prognosis (mortality rate 54.5%); however, the frequency or duration of arrhythmias was not determined in this group nor in the patients with arrhythmias only. Ambulatory electrocardiographic monitoring was not performed routinely in all patients in search of an arrhythmia; therefore, total information could be

Table VI Comparison of biopsy and autopsy findings in 19 patients

Tissue diagnosis	No of patients (%)	Time interval in months (mean)
Same diagnosis	9 (47.4)	0.5-90 (40.5)
New diagnosis (biopsy or autopsy)	10 (52.6)	2.8 (5.2)

limited. Patients with shortness of breath, palpitations, chest wall pain, and fatigue had a mortality rate of 38%. Perhaps the history was inaccurate or arrhythmias or congestive failure were undetected, but the findings suggest these symptoms cannot be predictive of a good prognosis. In contrast, those without symptoms, angina pectoris only, and arrhythmias only had a favorable course.

The influence of alcohol on eight patients is difficult to determine. There were no distinctive physical findings; however, in two patients there were questionable cloven and spinous T wave deformities. CR leads suggested by Evans were not recorded. Congestive heart failure was common (50%). The incidence was slightly lower in the nonalcoholic group (38%) but the cardiac mortality rate was similar in both groups (37.5% and 33.5% respectively). Others have reported that the groups cannot be separated by the mortality rates.<sup>11</sup> In patients with alcoholic cardiomyopathy, congestive failure was reported by Tobin and co-workers<sup>1</sup> in 31 of 39 patients (79.4%) and in all of the 48 patients evaluated by McDonald and associates<sup>2</sup> because it was the criterion for admission to the study. The cardiac mortality rate in these two reports was 20.6% and 39.5% respectively, not unlike our experience. The histologic appearance of biopsy specimens failed to distinguish between the groups. Except for the groups having no small vessel disease or no pathologic diagnosis, the same changes have been demonstrated by others.<sup>12,13</sup> The identical morphologic changes of biopsy and postmortem specimens of myocardium in a single patient who admitted to an excessive use of alcohol are similar to the experience reported by Szanto and Meister.<sup>14</sup>

Histologic findings have rarely provided a cause for myocardial disease, and it has been dis-

pointing in determining the management. The clinical course and survival depend on many factors and to be sure it is difficult to relate to a myocardial biopsy, but several observations from the study are of interest. Myocardial hypertrophy may not favorably influence prognosis. This is suggested by a cardiac mortality rate almost five times higher in the group with hypertrophy (biopsy, ECG or both) and no fibrosis. Electrocardiographic evidence of hypertrophy (left ventricular hypertrophy) was present when there was ST segment depression in Leads  $V_1$  and  $V_2$ , diphasic or inverted T waves and delayed intrinsoid deflections (0.05 sec or more). Electrocardiograms were recorded on high fidelity photographic machines (Sanborn Twin Beam). This is contrary to observations made by other investigators.<sup>1,2</sup> The different results could be explained by methods used for recognizing hypertrophy (ECG and angiograms), degree of cavity dilatation or hypertrophy or both and congestive heart failure. In 18 patients with congestive failure the mortality rate was 50% in the groups with and without hypertrophy and no fibrosis (patients with amyloid excluded). Another possibility is the presence of biochemical defects in the hypertrophic heart that are considered to contribute to reduced contractility. As expected hypertrophy (biopsy or ECG or both) and fibrosis and fibrosis without hypertrophy was associated with a high mortality rate (52% and 36% respectively).

The role of small arteries of the heart as the cause of various clinical syndromes has interested many investigators.<sup>3-7</sup> James and Fish<sup>3</sup> have studied extensively the small arteries (100 to 1 000 microns) in humans and concluded that wide spread involvement could be a cause of idiopathic cardiomyopathies. Evaluation of the anatomic features and the clinical events has suggested that narrowing of multiple small arteries could cause chest pain that resembles angina pectoris, arrhythmias and conduction disturbances (syncope and sudden death) and generalized cardiac enlargement with and without congestive heart failure. In 1974 Kannel and co-workers<sup>4</sup> suspected small vessel disease as the cause of congestive heart failure in a group of diabetic patients in the Framingham study. In the same year Hamby and associates<sup>5</sup> found subendothelial proliferation and fibrosis in small coronary

arteries in a similar group of patients and incriminated these changes as an etiologic factor in heart disease. Small vessel disease has been considered to be a possible cause of many of the features of the mitral valve prolapse syndrome.<sup>6,7</sup> It seems difficult to derive from biopsies the prevalence and significance of small vessel disease. The one or two specimens (closed chest technique) of the septum or ventricular wall are of limited value in patients with focal lesions and do not permit evaluation of sinus node or atrioventricular node arteries. Small vessel disease shown in biopsy studies (patients with amyloid excluded) in six of 139 patients (4.3%) and in one of 19 patients at autopsy (5.3%) would suggest that an anatomic abnormality of the small arteries is infrequent. Only one or two vessels in the biopsy specimens were affected. Because the clinical events were ventricular arrhythmias (two patients), chest wall pain (two patients), shortness of breath (one patient) and no symptoms (one patient), the findings probably excluded a generalized or diffuse process and played a minor role. Narrowing of small coronary arteries in two of four patients with sudden death could be significant, but difficult to prove. The meaning of multiple intravascular thrombi of small arteries (postmortem) in the single patient with congestive failure is unknown. The absence of structural changes in the microcirculation of 12 patients with diabetes mellitus (two autopsies) does not correspond with other observations.<sup>1,2</sup> On the other hand James<sup>3</sup> recognized normal small arteries in some diabetic subjects and had difficulty in providing an explanation. Angina pectoris in 28 patients without small vessel disease and the absence of this clinical syndrome in six patients with small coronary artery disease is noteworthy.

Myocardium with no pathological diagnosis in 35 of 139 patients (25%) probably means that focal changes were missed by the biopsy technique. Although a negative biopsy does not absolutely exclude myocardial disease, it was associated with a low cardiac mortality rate. The survival curve remains flat after two years. The decreased incidence of congestive failure (17%) and cardiac mortality rate (17%) compared to those with abnormal biopsies (46 and 60% respectively) would suggest that patchy histologic changes are present and possibly predictive of an improved

prognosis. A comparison of the biopsy and autopsy histological material revealed the same findings in less than one half of the 19 patients. The average interval of time between the biopsy and autopsy examination was similar in the two groups. Consequently, the patchy distribution of various histologic changes known to be present in cardiomyopathies provides the best explanation for the variable findings in some patients. In two patients only, the biopsy diagnosis was myocardium with no pathologic diagnosis and on post mortem examination 13 and 31 months post biopsy there was hypertrophy and hypertrophy and fibrosis respectively. In the other eight patients with a new diagnosis myocardial hypertrophy or fibrosis or both were present in the biopsy and autopsy specimens. Because these findings were associated with a high mortality rate the differences in the biopsy and autopsy diagnosis would not seem to be important.

### Summary

The purpose of this study was determination of the prognostic value of clinical and tissue (biopsy) findings of 139 patients with cardiomyopathy. The types of cardiomyopathy were congestive (113 patients) and hypertrophic or obstructive (26 patients). The mean follow up period of all patients was 4.3 years. Follow up of the survivors was between 13 months and 11.9 years, mean 5.4 years. Of the 47 cardiac deaths (33.8%) the minimum and maximum follow up was two weeks and 7.5 years respectively (mean 2.1 years). Patients with congestive heart failure had the highest five year cardiac mortality rate (51.8%). Coexisting cardiac arrhythmia had no influence on prognosis and an arrhythmia only was benign in most patients. Myocardial hypertrophy or fibrosis or both and myocardium with no pathologic diagnosis had prognostic value. Small vessel disease was infrequent and not associated with specific clinical manifestations.

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# Effects of vasodilators on pulmonary hemodynamics and gas exchange in left ventricular failure

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Sodium nitroprusside is a potent vasodilator that has been widely used to treat hypertensive crises and congestive heart failure and to produce controlled hypotension during surgery. Previous studies have demonstrated reduced arterial oxygen tension when nitroprusside is infused to produce controlled hypotension during surgery and when it is given to patients maintained on assisted respiration immediately following coronary artery surgery. This hypotensive effect may also occur in patients with congestive heart failure despite concomitant reduction in pulmonary capillary pressure.

Several non parenteral vasodilators including hydralazine and nitrates have also been used in congestive heart failure but their effects on arterial oxygen tension have not been studied. Nitrates have a prominent venodilator effect whereas hydralazine dilates primarily arteries. Combining these two agents results in hemodynamic effects similar to those of nitroprusside: an arterial and venous dilator. The present study was designed to further elucidate the mechanisms of nitroprusside induced hypoxemia by measuring

lung blood gases, lung mechanics and cardiopulmonary hemodynamics in patients with congestive heart failure. In addition the effects of hydralazine and hydralazine combined with isosorbide dinitrate were similarly evaluated not only to determine their effects on arterial oxygen tension but also to correlate changes in oxygenation with the various hemodynamic responses produced.

## Methods

Ten male patients with clinical and radiographic evidence of left ventricular failure were selected for study. In six of the patients the left ventricular failure was due to ischemic heart disease and in the other four to primary cardiomyopathy. All patients were functional Class III or IV (New York Heart Association criteria) while on standard treatment with digitalis and diuretics. Their ages ranged from 39 to 79 years with a mean age of 58 years. Patients with valvular heart disease (other than functional mitral insufficiency), severe primary pulmonary disease (defined as resting arterial  $PO_2 < 50$  mm Hg or  $PCO_2 > 50$  mm Hg) or patients in shock were excluded from the study.

On the day of study all diuretics and vasodilators were withheld so that a relatively steady state existed prior to the administration of test drugs. Patients receiving maintenance digitalis therapy or oral antiarrhythmic agents were given their daily doses of these drugs.

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Mean pulmonary artery wedge pressure (mm. Hg)					Cardiac index (L/min./M <sup>2</sup> )				
C	VP	RC	H	H+N	C	VP	RC	H	H+N
31	19	31	24	20	22	23	22	27	31
29	10	31	25	10	32	34	28	28	37
2	24	28	31	26	18	24	18	21	23
23	18	30	19	16	19	21	17	25	25
25	11	27	19	8	21	34	26	55	47
15	9	14	14	8	20	21	20	28	25
35	21	33	38	40	13	18	14	21	23
37	24	30	31	23	24	35	24	27	37
38	21	26	24	18	27	43	27	38	37
20	12	24	24	20	19	30	21	30	28
269	16.7	269	249	189	213	281	210	299	314
21	1.9	18	2.2	3.1	016	0.26	014	0.37	0.27
	< .001		NS	< .01		< .01		< .01	< .001

Arterial pH					Calculated arterial oxygen saturation (%)					Measured arterial oxygen content (volumes %)				
C	VP	RC	H	H+N	C	VP	RC	H	H+N	C	VP	RC	H	H+N
74	7.42	7.43	7.53	7.56	96	96	96	97	96	—	—	—	—	—
747	7.49	7.47	7.47	7.46	96	94	94	96	91	—	—	—	—	—
741	7.51	7.53	7.47	7.49	97	96	97	96	96	13.6	12.7	13.5	13.0	12.5
749	7.40	7.45	7.53	7.52	96	89	96	97	97	14.3	13.2	—	—	—
41	7.41	7.40	7.59	7.49	96	95	96	97	96	16.3	15.7	16.5	16.5	15.5
43	7.43	7.41	7.42	7.41	97	92	96	97	97	16.3	15.7	16.0	15.8	15.4
744	7.46	7.47	7.54	7.53	96	94	97	96	97	13.7	13.0	13.6	14.5	13.9
757	7.53	7.54	7.53	7.54	97	97	97	97	97	16.9	15.6	16.5	16.6	16.7
747	7.47	7.47	7.42	7.47	86	71	81	78	83	15.0	12.1	13.9	13.9	16.4
759	7.56	7.54	7.6	7.59	97	95	97	97	96	13.8	12.7	14.7	13.8	13.3
7469	7.463	7.466	7.497	7.507	95.1	91.6	94.6	93.7	94.7	15.0	13.8	14.9	14.9	14.7
017	0.18	0.18	0.16	0.17	1.0	2.4	1.5	1.9	0.9	0.47	0.59	0.57	0.54	0.57
	NS		NS	< .05		< .05		NS	NS		< .05		NS	NS

$$Q/Q = \frac{C_c O - C_a O}{C_c O - C_v O}$$

where  $C_c O$  = O content of pulmonary capillary blood obtained from the arterial pH and the calculated  $P O_2$

$C_a O$  = systemic arterial O content

$C_v O$  = O content of mixed venous blood where the O contents were calculated from the product of hemoglobin per cent oxygen saturation and 1.34

The ratio of dead space to tidal volume ( $V_D/V_T$ ) was calculated by

$$V_D/V_T = \frac{P_a CO - P_v CO}{P_a CO}$$

where  $P_a CO$  =  $P_a CO$  of expired air

Oxygen delivery index ( $O DI$  in cc/min/M<sup>2</sup>) was calculated as the product of cardiac index and arterial oxygen content

Statistical analysis was performed using Stu

Table 1 Hemodynamic effects of nitroprusside hydralazine and hydralazine-nitrate combination in heart failure

Patient no	Heart rate (beats/min)					Mean systemic arterial pressure (mm Hg)					Mean pulmonary artery pressure (mm Hg)				
	C	NP	RC	H	H+N	C	NP	RC	H	H+N	C	NP	RC	H	H+N
1	84	81	84	93	93	83	67	83	72	68	37	28	37	36	31
2	84	75	78	81	81	72	65	68	68	63	34	16	31	34	34
3	63	67	69	72	75	77	58	74	77	60	37	32	37	40	37
4	98	90	87	99	100	80	64	68	60	55	30	22	38	24	18
5	93	93	90	101	102	79	74	80	64	60	37	18	33	30	1
6	85	81	83	89	90	80	72	78	78	73	24	13	23	23	15
7	81	77	77	90	101	88	70	86	85	77	30	39	52	57	57
8	84	72	72	84	81	87	60	75	82	68	51	30	40	41	36
9	111	102	108	111	108	110	74	105	87	78	40	27	36	33	28
10	86	81	90	96	90	83	75	95	89	81	28	21	37	26	26
mean	88.0	81.9	83.8	91.6	92.6	83.9	68.4	81.2	76.2	69.3	36.8	25.3	36.7	36.0	33.1
SEM	3.7	3.3	2.5	3.5	3.6	3.3	1.8	3.7	3.2	2.9	2.8	1.6	2.3	1.9	3.1
p	< .001					< .001					< .001				

C = control NP = nitroprusside RC = recontrol H = hydralazine H+N = hydralazine plus nitrate  
 = NP compared to C H compared to RC and H+N compared to RC

Table 2 Effects of nitroprusside hydralazine and hydralazine-nitrate combination on blood gases in heart failure

Patient no	Arterial PO (mm Hg)					Arterial PCO (mm Hg)					Venous PO (mm Hg)				
	C	NP	RC	H	H+N	C	NP	RC	H	H+N	C	NP	RC	H	H+N
1	77	80	77	80	80	22	23	22	17	17	27	30	27	30	31
2	3	6	6	82	58	30	34	37	28	38	31	35	31	34	31
3	9	71	84	73	71	40	36	30	40	39	28	29	28	28	28
4	78	6	8	72	64	28	33	33	29	28	26	28	27	33	30
5	87	6	84	86	82	31	35	34	31	29	36	42	38	43	39
6	80	60	80	91	70	32	31	33	33	32	33	31	35	38	38
7	71	68	80	73	62	34	35	32	25	27	25	30	23	26	26
8	80	66	82	76	84	30	32	30	31	28	26	33	28	37	36
9	52	43	47	45	51	45	47	48	47	42	29	27	26	27	27
10	76	63	70	75	70	37	38	41	37	36	28	32	23	30	31
mean	75.3	64.9	75.1	74.9	69.8	33.6	34.4	34.6	31.7	31.6	28.9	31.6	28.4	32.5	31.6
SEM	3.1	3.3	3.7	4.1	3.5	2.0	1.9	2.2	2.6	2.3	1.2	1.3	1.6	1.6	1.4
p	< .01					NS					< .001				

C = control NP = nitroprusside RC = recontrol H = hydralazine H+N = hydralazine-nitrate combination  
 = NP compared to C H compared to RC and H+N compared to RC

the interventions in each. Per cent oxygen saturation was calculated from the PO and pH using an Instrumentation Laboratories pH blood gas calculator. Alveolar-arterial oxygen difference (A-a gradient) in mm Hg was calculated according to the formula

$$A-a = P_{AO} - P_{AO}$$

where  $P_{AO}$  = arterial PO and  $P_{AO}$  (PO of alveolar air) is calculated from the alveolar gas equation

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[ \frac{P_{ACO_2}}{R} F_{IO_2} (1-R) \right]$$

with  $P_{IO_2}$  = inspired oxygen tension  $P_{ACO_2}$  = alveolar PCO (assumed equal to arterial PCO)  $F_{IO_2}$  = fraction of O<sub>2</sub> in inspired air = 0.209  $R$  = respiratory quotient (assumed = 0.8) Venous admixture ( $Q/Q$ ) was calculated as

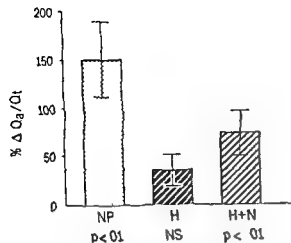


Fig 3 Per cent change in venous admixture ( $Q_v/Q_t$ ) produced by nitroprusside (NP), hydralazine (H) and hydralazine-nitrate combination (H+N). P values are given for comparing NP to control II to recontrol and H+N to recontrol. Horizontal bars indicate mean  $\pm$  SEM.

P O with isosorbide dinitrate did not quite reach the  $p < 0.05$  criteria for statistical significance ( $t = 2.1954$ ,  $p < 0.06$ ). Since the P O decreased with nitroprusside so did the calculated arterial oxygen saturation. However, due to the non-linear relationship between P O and oxygen saturation, the changes in oxygen content were of a much lower magnitude. The values of arterial oxygen content measured directly paralleled the changes in O saturation but unfortunately these values were not available for every patient.

The A-a gradient (Fig 2) increased significantly with nitroprusside but not with hydralazine alone. When isosorbide dinitrate was added the increase in A-a gradient again became significant. The changes in  $Q_v/Q_t$  paralleled those of the A-a gradient and Fig 3 shows the per cent change in  $Q_v/Q_t$  which occurred with each regimen. All of the patients had an increase in  $Q_v/Q_t$  with nitroprusside and  $Q_v/Q_t$  increased in nine of the ten patients with hydralazine plus isosorbide dinitrate but no significant changes occurred with hydralazine alone.

The P O of mixed venous blood increased with all the drug regimens reflecting the increase in cardiac output. There was a slight decrease in arterial P CO ( $P_{CO_2}$ ) with a concomitant increase in arterial pH after hydralazine and hydralazine-isosorbide dinitrate combination. Although this decrease in P CO was small and only became statistically significant on the hydralazine-isosorbide dinitrate combination, most of the decrease from recontrol levels had already

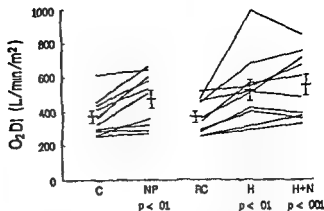


Fig 4 Changes in oxygen delivery index (O<sub>2</sub> DI) produced by nitroprusside (NP), hydralazine (H) and hydralazine-nitrate combination (H+N). P values are given for comparing NP to control II to recontrol and H+N to recontrol. Horizontal bars indicate mean  $\pm$  SEM.

occurred on the hydralazine alone. This effect was not seen during nitroprusside infusion.

Since the O<sub>2</sub> DI (Fig 4) increased with all of the regimens, it is evident that the rise in cardiac output compensated for the fall in P O such that oxygen delivery was not compromised. This was true even in the patient with the most severe hypovolemia. This patient had a control P O of 52 mm Hg that fell to 43 mm Hg on nitroprusside. Despite this low level of P O, his O<sub>2</sub> DI went from 440 to 577 cc/min/m².

**Pulmonary function tests.** As seen in Table III, no significant changes from control values were found in any of the pulmonary function tests (VC, V<sub>T</sub>, V<sub>E</sub>, V<sub>m</sub>, FEV<sub>1</sub>, and SBN III) with any of the drugs. In addition, the V<sub>E</sub>/V<sub>T</sub> did not change with any of the drugs in those eight patients for whom it could be calculated.

From the above data, it appears that the major effects on arterial oxygenation occur with the drugs that have the most prominent pulmonary vascular effects (i.e. with nitroprusside and when isosorbide dinitrate is added to hydralazine but not with hydralazine alone). Fig 5 shows the correlation between change in A-a gradient and change in PAR. The correlation coefficient of this comparison is  $-0.57$ , which is significant at the 1 per cent level.

## Discussion

This study confirms the findings of Mookherjee and associates that a decrease in arterial P O occurs when patients with congestive heart failure are treated with nitroprusside. This fall in P O occurs concomitant with an increase in A-a

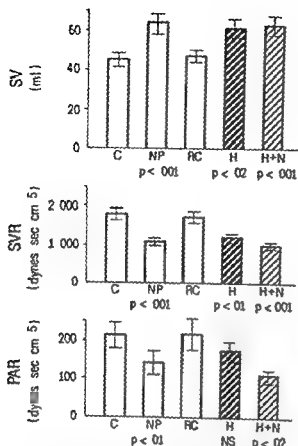


Fig 1 Changes in stroke volume (SV), systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) produced by nitroprusside (NP), hydralazine (H) and hydralazine nitrate combination (H+N). P values are given for comparing NP to control (C), H to recontrol (RC) and H+N to RC.

dent = paired t test. Data are presented as mean  $\pm$  standard error of the mean. Differences are considered statistically significant for p values less than 0.05.

## Results

**Hemodynamics** Hemodynamic responses to the different regimens are shown in Table I and Fig 1 presents the resultant effects on stroke volume (SV), SVR and PAR. Nitroprusside increased CI and decreased PA and PAW pressure, mean systemic blood pressure (BP) and heart rate. SV was increased while SVR and PAR decreased. All hemodynamic parameters returned to the initial control levels after nitroprusside infusion was stopped except for a small but statistically significant decrease in heart rate.

Hydralazine produced an increase in CI of 0.9 L/min/M and a fall in BP of 7.0 mm Hg without altering PA or PAW. Heart rate increased modestly by 8 beats/minute. As a result SV increased and SVR decreased but the

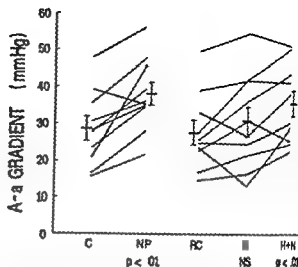


Fig 2 Changes in A-a gradient produced by nitroprusside (NP), hydralazine (H) and hydralazine-nitrate combination (H+N). P values are given for comparing NP to control, H to recontrol, and H+N to recontrol. Horizontal bars indicate mean  $\pm$  SEM.

small decrease in PAR was not significant.

When isosorbide dinitrate was added to hydralazine the most significant changes were a decrease in PA and PAW resulting in a decrease in PAR of 61 dynes/cm<sup>2</sup> from the level on hydralazine alone. In addition there was a further 7 mm Hg decrease in BP and 180 dynes/cm<sup>2</sup> decrease in SVR with essentially no additional increase in heart rate. Except for a slight difference in heart rate there was no significant difference between the effects of hydralazine-isosorbide dinitrate combination and nitroprusside.

Heart rate-systolic blood pressure product as index of myocardial oxygen consumption was not increased by any of the regimens. From a control of  $10,400 \pm 952$  (mean  $\pm$  SEM) it decreased with nitroprusside to  $8,440 \pm 574$  ( $p < 0.01$ ). The values on hydralazine ( $9,570 \pm 1212$ ) and on hydralazine-nitrate combination ( $9,630 \pm 671$ ) were not significantly different from the post-nitroprusside recontrol value of  $9,840 \pm 862$ .

**Blood gases** Table II summarizes the effects on blood gases of the different drugs and Figs 3 through 4 show the changes in A-a gradient,  $\text{O}_2/\text{Q}$  and  $\text{O}_2/\text{DI}$ . There are no significant differences in any of these variables between the initial control and the post nitroprusside recontrol values.

$\text{P O}_2$  fell significantly during nitroprusside infusion but not with hydralazine alone. When isosorbide dinitrate was added to hydralazine the  $\text{P O}_2$  dropped by 5.1 mm Hg. Compared to the post nitroprusside recontrol value this decrease in

combination despite the increase in A-a gradient

Other vasodilators which affect pulmonary vasculature have also been shown to affect P O<sub>2</sub>. Majid and colleagues<sup>1</sup> used phentolamine to decrease the pulmonary arterial and pulmonary artery wedge pressures and increase the cardiac output in patients with severe heart failure. They observed a decrease in P O<sub>2</sub> from  $72 \pm 5$  to  $66 \pm 5$  mm Hg with the drug infusion at rest and from  $73 \pm 7$  to  $66 \pm 7$  mm Hg with the drug during exercise. In their patients unable to exercise the P O<sub>2</sub> decreased from 64 to 60 mm Hg in the first five minutes of drug infusion. A similar effect was noted by Courmand and colleagues<sup>2</sup> using selective infusion of acetylcholine into one branch of the pulmonary artery as a vasodilator. Although Fritts and co-workers<sup>3</sup> found no change in arterial oxygen saturation when infusing acetylcholine into the pulmonary artery of patients on 21 per cent oxygen they did note a decrease when the patients were on 12 per cent oxygen.

The fall in P O<sub>2</sub> produced by nitroprusside has previously been attributed to an increase in venous admixture resulting from an altered ventilation/perfusion relationship in the lungs. Our observations support this, as the calculated venous admixture increased significantly with nitroprusside infusion and returned to control when it was stopped. No changes were found however in pulmonary mechanics. It is possible that other methods of determining pulmonary ventilation and perfusion abnormalities such as radioisotope or inert gas washout techniques would detect changes not apparent in our data. Nonetheless our data do suggest that the major alterations in ventilation/perfusion occurred due to redistribution of flow rather than to changes in ventilation. The same mechanism is likely for the increase in A-a gradient produced by hydralazine plus isosorbide dinitrate.

Although time limitations precluded the testing of isosorbide dinitrate alone it is known that isosorbide dinitrate does have a pulmonary vascular effect which hydralazine lacks. Thus an increase in A-a gradient and venous admixture might be expected to occur with isosorbide dinitrate alone in the absence of hydralazine effect. This hypothesis is supported by the finding that the closely related compound nitroglycerin has been shown to produce hypoxemia.

From the above considerations it is reasonable to postulate that vasodilators which affect the

pulmonary vasculature act indiscriminately to dilate all pulmonary vessels including those perfusing poorly ventilated alveoli. This would alter the physiologic vasoconstrictor response which decreases blood flow to hypoventilated alveoli and thus upset the normal ventilation/perfusion balance. This becomes manifest by an increase in venous admixture and A-a gradient.

Other possible mechanisms for the decrease in P O<sub>2</sub> appear less likely. Hypoventilation is adequately ruled out by the lack of any increase in arterial PCO<sub>2</sub>. Indeed it is of interest that there was a small decrease in PCO<sub>2</sub> with a concomitant small increase in arterial pH when hydralazine was given that persisted when isosorbide dinitrate was added. This decrease in PCO<sub>2</sub> is unlikely a response to hypoxia as little fall in P O<sub>2</sub> occurred with hydralazine and no similar decrease in PCO<sub>2</sub> occurred with nitroprusside despite the decrease in P O<sub>2</sub> produced by that drug.

Since an increase in cardiac output occurs with these vasodilators it might be postulated that the transit time of blood in the lung is decreased such that it is not in contact with the alveolar gas exchange area long enough to become fully saturated. This would appear unlikely since full oxygen saturation is considered to occur in the early portion of the alveolar capillaries with adequate safety margin so that desaturation does not occur with the increase in cardiac output. In addition hydralazine would be expected to increase A-a gradient similar to the other two drug regimens if this mechanism were operational but A-a gradient did not change with hydralazine.

Another mechanism which could be considered is interference with biochemical reactions involving oxygen transport. However it is unlikely that biochemical effects on hemoglobin function can account for the observed responses. Although the metabolites of nitroprusside (cyanide and thio cyanate) could be incriminated as possible effectors of hemoglobin function similar compounds are not produced by the hydralazine plus isosorbide dinitrate combination which produced similar effects on A-a gradient and hemodynamics.

Although oxygen delivery was enhanced in all of our patients on vasodilators we do not know the organ distribution of this increased flow. It is possible that some vascular beds may suffer from a lower oxygen content more than others due to redistribution of arterial blood. Since the

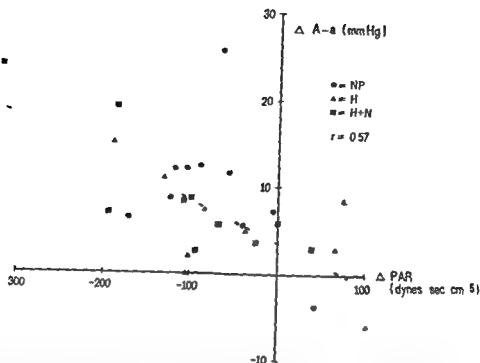


Fig 3 Correlation of change in alveolar-arteriolar oxygen gradient ( $\Delta A-a$ ) with change in pulmonary arteriolar resistance ( $\Delta PAR$ ) with nitroprusside (NP) hydralazine (H) and hydralazine plus isosorbide dinitrate (H+N). Correlation coefficient ( $r$ ) =  $-0.57$  which is significant at the 1 per cent level

Table III Effects of nitroprusside hydralazine and hydralazine-nitrate combination on pulmonary function tests in heart failure (mean  $\pm$  SEM)

	Control	Nitroprusside	Hydralazine	Hydralazine Nitrate
FEV <sub>1</sub>	19 $\pm$ 21	20 $\pm$ 20	19 $\pm$ 20	20 $\pm$ 20
III SBN	69 $\pm$ 261	69 $\pm$ 214	73 $\pm$ 260	82 $\pm$ 41
VC	31 $\pm$ 20	30 $\pm$ 30	29 $\pm$ 73	29 $\pm$ 34
	40 $\pm$ 900	34 $\pm$ 051	50 $\pm$ 144	58 $\pm$ 147
V <sub>1/2</sub>	10 $\pm$ 36	13 $\pm$ 23	17 $\pm$ 40	17 $\pm$ 49
V <sub>1/4</sub>	41 $\pm$ 61	39 $\pm$ 50	41 $\pm$ 57	42 $\pm$ 62
V <sub>1/8</sub>	46 $\pm$ 041	40 $\pm$ 257	39 $\pm$ 038	41 $\pm$ 033

FEV<sub>1</sub> = forced expiratory volume at 1 sec in liters (10 patients) III SBN = slope of phase III of the single breath nitrogen test in % N/liter (10 patients) VC = vital capacity in liters (10 patients) V<sub>1/2</sub> = flow at 25% of VC in liters/sec (10 patients) V<sub>1/4</sub> = flow at 50% of VC in liters/sec (10 patients) V<sub>1/8</sub> = peak flow in liters/sec (10 patients) V<sub>1/8</sub> = r to of d and space to total volume (10 patients) None of the variables are significantly different from control with any of the drug regimens.

gradient. Despite the decrease in P O<sub>2</sub> and increase in A<sub>1</sub> gradient, cardiac output improves such that calculated oxygen delivery is enhanced. In addition, this study demonstrates that although hydralazine produces an equivalent increase in cardiac output, it has very little pulmonary vascular effects compared to nitroprusside. Thus hydralazine has minimal effect on pulmonary artery pressure, left ventricular filling pressure, and PAR. Also, unlike nitroprusside, hydralazine lacks any significant effect on P O<sub>2</sub> or A<sub>1</sub> gradient.

When isosorbide dinitrate is combined with hydralazine, the venous and pulmonary vascular effects of the nitrate decrease pulmonary arterial pressure, left ventricular filling pressure, and PAR, such that hemodynamic effects similar to nitroprusside are obtained. Also similar to nitroprusside, an increase in A<sub>1</sub> gradient is produced by the combination of hydralazine and isosorbide dinitrate. Thus nitroprusside and the combination of hydralazine plus isosorbide dinitrate decrease PAR and increase A<sub>1</sub> gradient. As with nitroprusside, oxygen delivery is enhanced by the

## The cyclic changes and structure of the base of the aortic valve

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The base of the aortic valve is a circumferential region at the proximal attachment of the aortic leaflets. It has been described as a fibrous annulus which suggests a ringlike nonexpansible structure. The base has been reported to undergo little or no dimensional change during the cardiac cycle.<sup>1</sup> Some investigators have stated that the annulus is not a continuous fibrous ring.<sup>2-4</sup> Others have speculated that the annulus does change dimensions and that it participates in aortic valve function.<sup>5</sup> Furthermore, the base of the aortic valve is continuous with the left ventricular outflow tract which changes in diameter during the cardiac cycle in humans<sup>6</sup> and in dogs.

The previous reports indicate a disagreement on the behavior of the base of the natural aortic valve. An accurate understanding of the behavior of the base is important. If it is a dynamic structure, its behavior will affect normal valvular function. Current prosthetic valves are fabricated with a nonexpansile sewing ring which is attached to the base of the aortic valve. If the base is a dynamic structure, the mismatch with the nonexpansile ring could cause occasional periprosthetic leaks or could interfere with function of the base.

The present study investigated the structure

and behavior of the base of the aortic valve in dogs in vivo under physiologic conditions.

### Materials and methods

Four dogs (20 to 30 kg) were anesthetized with intravenous pentobarbital (25 mg/kg) and placed on total cardiopulmonary bypass. Through an aortotomy, small platinum markers (1 mm x 1 mm and 10 mg weight) were attached to the annulus at the base of each aortic leaflet. Small tantalum clips were also placed at the center of the free edge of two leaflets. The position of the markers is shown in Fig 1. The dogs were allowed to recover and were studied repeatedly over several weeks.

During each study, the dogs were lightly anesthetized and were positioned under an x-ray tube with an image intensifier. During fluoroscopy, the movements of the markers in the beating heart were recorded on videotape at a rate of 60 fields/second. The marker movement was recorded first with the x-ray beam parallel to the axis of the aorta (with the base markers projected in a triangle) and then with the x-ray beam perpendicular to the axis of the aorta (with the base markers projected in a straight line). Using these two projections it was possible to eliminate any error due to rotation or yaw of the aortic root. The dog was then rotated 180 degrees on its spinal axis and the two new projections were recorded. This enabled elimination of error due to movement of the aortic root toward or away from the image intensifier during the cardiac cycle. The pressures in the ascending aorta and in the left ventricle were recorded using 7F pigtail catheters. The EKG (Lead II) was also recorded simulta-

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decreases in oxygen content we observed are small this is unlikely to become clinically important except perhaps in patients with a very low initial  $\text{PO}_2$ . Our patients had an increase in cardiac output with vasodilators but this might not occur in patients with initially normal cardiac outputs. The possibility of significant global or regional hypoxia should thus be considered and blood gases should be monitored when vasodilators with prominent pulmonary vascular effects are used in patients who have a very low arterial  $\text{PO}_2$  and/or in whom no increase in cardiac output is expected.

### Summary

Nitroprusside (NP) has been shown to improve left ventricular function in patients with congestive heart failure but despite an increased cardiac output and decreased pulmonary capillary pressure, arterial oxygen tension ( $\text{PO}_2$ ) may fall. In order to determine the mechanism of this hypoxemia and to determine if similar effects occur with non parenteral vasodilators hemodynamic respiratory and blood gas responses to NP hydralazine (H) and hydralazine combined with isosorbide dinitrate (H+N) were studied in 10 patients with left ventricular failure. At the dosages used all three drug regimens increased cardiac output equivalently but pulmonary vascular responses differed. NP and H+N decreased mean pulmonary artery pressure, pulmonary wedge pressure and pulmonary arteriolar resistance while H did not. NP decreased  $\text{PO}_2$  by 104 mm Hg ( $p < 0.01$ ) and H+N decreased it by 53 mm Hg ( $p < 0.06$ ) while H did not alter  $\text{PO}_2$ . Arteriole-arteriolar oxygen gradient increased with NP ( $150 \pm 39$  per cent  $p < 0.01$ ) and with H+N ( $73 \pm 23$  per cent  $p < 0.01$ ) but not H alone ( $51 \pm 16$  per cent). Similarly per cent change in venous admixture increased on NP ( $28.7 \pm 3.3$  to  $38.5 \pm 3.1$  per cent  $p < 0.01$ ) and H+N ( $28.1 \pm 3.3$  to  $36.8 \pm 3.5$  per cent  $p < 0.01$ ) but not H alone ( $28.1 \pm 3.3$  to  $31.5 \pm 4.1$  per cent). There was no increase in arterial carbon dioxide tension or change in pulmonary function studies with any of the drugs. Due to the increase in cardiac output oxygen delivery index (cardiac output times arterial oxygen content) increased with each regimen despite the changes in  $\text{FO}_2$ . Changes in arteriole-arteriolar oxygen gradient correlate

with the changes in pulmonary arteriolar resistance. Thus vasodilators which have prominent pulmonary vascular effects can decrease  $\text{PO}_2$  in patients with congestive heart failure. This effect is most likely due to increasing ventilation-perfusion inequities.

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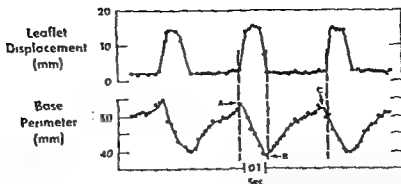


Fig 2 Phasic plot of leaflet displacement (the distance between the two leaflet markers) and base perimeter (perimeter of a triangle formed by the base markers) versus time. The base perimeter is maximum (point A) in early systole. The perimeter decreases (A to B) in systole and increases (B to C) in diastole.

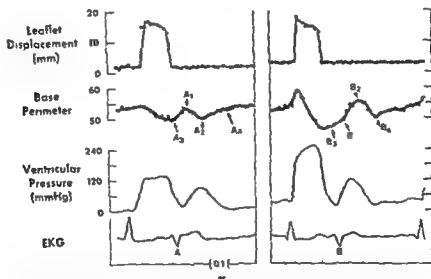


Fig 3 Phasic plot of leaflet displacement, base perimeter, corresponding ventricular pressure, and EKG versus time for two separate recordings. Two normal heartbeats and two ectopic beats (A and B) are shown. For the normal beats the base perimeter decreases during systole. For ectopic beat A the perimeter decreases (A to A') but for ectopic beat B the perimeter increases (B to B') during systole. Base perimeters were greater after the ectopic beats (A' and B') than before the beats (A and B).

pressure was varied over a wide range the change in the perimeter also varied. In four dogs when the pressure was varied from 70/0 to 280/216 mm Hg, the change in the perimeter ranged from 5% to 28% (Table I).

With premature ventricular contractions the behavior of the base could vary from that observed in normal cardiac cycles (Fig 3). During ectopic beat A the base perimeter decreased from A to A' (during systole). During B the perimeter increased from B to B' (during systole). The ventricular pressure increased in both instances. During both ectopic beats no blood was ejected

(the leaflets did not open) and the base perimeter was greater after these ectopic beats (A' and B') than before (A and B). The base perimeter increased in every dog as the ventricular diastolic pressure increased (Fig 4).

Histologic examination of the aortic root indicated that the structure would permit the dimensions of the base to change during the cardiac cycle. Transverse sections of the root showed that contractile tissue either musculoblastic tissue or myocardium comprises portions of the root at the base. For example, a section through the middle of the root which illustrated all parts of

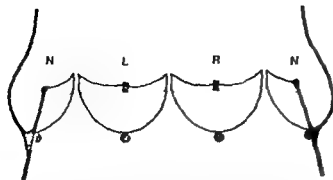


Fig 1 Aortic valve exposed by a vertical incision through the noncoronary sinus. *L*, *R* and *N* are the leaflets corresponding to the left, right and noncoronary sinuses respectively. Dotted line shows the level of leaflet coaptation. Three radiopaque markers at the base of the leaflets are represented by closed circles. Two radiopaque markers at the center of the free edge of the left and right coronary sinus leaflets are represented by vertical bars.

neously with the videotape recording. The systemic pressure was raised by infusing angiotensin or lowered by infusing nitroprusside and the studies were repeated.

The movement of the leaflets and dimensional changes of the base were obtained by analysis of the movement of the markers. The videotapes were analyzed field by field in a stop motion display mode on a television screen. In the first projection recorded with the x-ray beam parallel to the axis of the aorta, the distance between the two leaflet markers was measured in each frame for three consecutive cardiac cycles. This distance was used as an indicator of a closed or opened valve. The perimeter of the triangle formed by the base markers was also measured and was used as an indicator of the dimensions of the base.

A typical graphic representation of the leaflet displacement plotted as the distance between two leaflet markers and the base perimeter versus time is shown in Fig 2. Each data point on these curves was obtained from a single videofield.

In the second projection recorded with the x-ray beam perpendicular to the axis of the aorta, the analysis of the movement of the markers was performed in a manner similar to that used for the first projection. Details of the analysis are given elsewhere. The movement of the leaflets and the dimensional changes in the base obtained from this projection were similar to those obtained from the first projection.

The structure of the base was studied histologically in canine aortic roots which were subse-

Table 1 Blood pressure vs base perimeter

Dog No	Blood pressure (mm Hg)	Base perimeter change
1	Aortic 120/60	27 ± 9
2	Aortic 127/90	16 ± 1.5
3	Aortic 113/78	88 ± 18
4	Femoral 108/87	96 ± 2
	Mean 115/78	Range 9 to 22
<b>Aortic blood pressure</b>		
1	70/50 260/160	5 10
2	94/48 255/150	10 16
	90/30 270/187	65 19
3	88/50 257/216	10 18
	120/60 240/210	90 98
4	70/47 280/156	1 28
	Range 70/50 280/216	Range 5 to 98

$$\text{Base perimeter \% change} = \frac{P_{\max} - P_{\min}}{P_{\min}} \times 100\%$$

(where  $P$  = perimeter)

ly sectioned and fixed in the closed position with glutaraldehyde at 100 mm Hg pressure. The sections were stained to show the distribution of collagenous elastic and muscular elements of the valve.

## Results

**Dimensional changes of the base.** The base of the aortic valve changed dimensions during each normal cardiac cycle (Fig 2). The base perimeter was maximal (point A) in early systole just prior to separation of the leaflets. The perimeter decreased (interval AB) during systole and was minimal (point B) at the end of systole just prior to approximation of the leaflets. The perimeter increased (interval BC) during diastole. This qualitative behavior of the base was observed consistently in all dogs and in all normal cardiac cycles.

The amount of the cyclic change in the base perimeter was calculated by measurement of the peak to peak values (A to B). The amount of cyclic change at normal systemic pressure was determined for each dog by taking an average of 24 to 36 cardiac cycles obtained from two to three separate studies. The amount of cyclic change at other systemic pressures was determined by taking an average of six to nine cardiac cycles obtained from two to three separate studies. The amount of change was different for different dogs at normal systemic pressure. In four dogs the change in the perimeter ranged from 9% to 92% (Table 1). In any one animal when the systemic

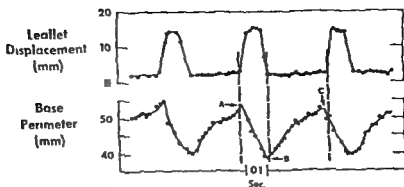


Fig 2 Phasic plot of leaflet displacement (the distance between the two leaflet markers) and base perimeter (perimeter of a triangle formed by the base markers) versus time. The base perimeter is maximum (point A) in early systole. The perimeter decreases (A to B) in systole and increases (B to C) in diastole.

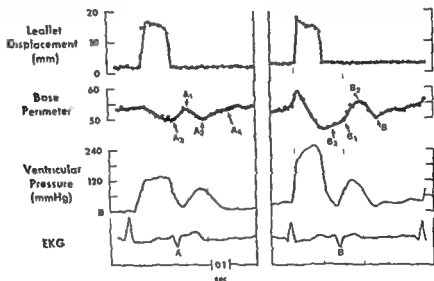


Fig 3 Phasic plot of leaflet displacement, base perimeter, corresponding ventricular pressure, and EKG versus time for two separate recordings. Two normal heartbeats and two ectopic beats (A and B) are shown. For the normal beats the base perimeter decreases during systole. For ectopic beat A the perimeter decreases (A<sub>1</sub> to A<sub>4</sub>) but for ectopic beat B the perimeter increases (B<sub>1</sub> to B<sub>2</sub>) during systole. Base perimeters were greater after the ectopic beats (A and B) than before the beats (A and B).

pressure was varied over a wide range, the change in the perimeter also varied. In four dogs when the pressure was varied from 70/50 to 280/216 mm Hg, the change in the perimeter ranged from 5% to 28% (Table 1).

With premature ventricular contractions the behavior of the base could vary from that observed in normal cardiac cycles (Fig 3). During ectopic beat A, the base perimeter decreased from A to A<sub>1</sub> (during systole). During B, the perimeter increased from B to B<sub>1</sub> (during systole). The ventricular pressure increased in both instances. During both ectopic beats, no blood was ejected

(the leaflets did not open) and the base perimeter was greater after these ectopic beats (A and B) than before (A and B). The base perimeter increased in every dog as the ventricular diastolic pressure increased (Fig 4).

Histologic examination of the aortic root indicated that the structure would permit the dimensions of the base to change during the cardiac cycle. Transverse sections of the root showed that contractile tissue, either musculoelastic tissue or myocardium, comprises portions of the root at the base. For example, a section through the middle of the root, which illustrated all parts of

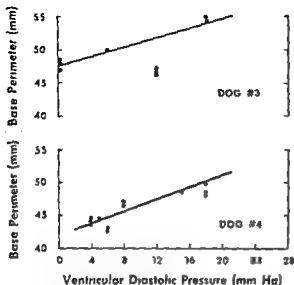


Fig 4 Base perimeter in diastole versus ventricular diastolic pressure for two dogs. The base perimeter increases as the ventricular diastolic pressure increases.

the valve (Fig 5 a) showed sinus walls composed principally of smooth muscle interwoven with elastic connective tissue fibers like the more distal wall of the aorta itself. Segments of wall between the sinuses (called intervalvular trigones by McAlpine<sup>11</sup>) are composed of dense collagenous tissue (d in Fig 5 a) or myocardium (Fig 5 a and c in Fig 5 b) plus a more internal cushion of very loose watery connective tissue (Fig 5, a and u in Fig 5 b). Much of this myocardial mass consists of circularly oriented fibers (c in Fig 5 b) some of which appear to be inserted into the sinus wall (Fig 5 b arrow). Contraction of this muscle tends to decrease the circumference of the root. More proximally toward the base of the valve two of the three trigonal regions consist almost entirely of obliquely or circularly oriented myocardium (c in Fig 6 a). Dense collagenous tissue present in these zones is limited to a thin intimal layer of tissue (t in Fig 6 b) internal to the loose connective tissue cushion (w in Fig 6 b) and continuous with the ventricular face of the valve leaflets. This tissue is neither as dense nor as thick as the major substances of the leaflets themselves. Only the trigonal region between the left coronary and the noncoronary sinuses which serves as the origin of a mitral valve leaflet is composed of dense collagenous tissue throughout the aortic root (Figs 5 a, 6 a, 7 a and d in Fig 7 b). At their bases where the markers were placed (Fig 7 ■ and l in Fig 7 b) the right and left coronary leaflets appear to be embedded in ven-

tricular muscle (c in Fig 7, a). Frequently the noncoronary leaflet is the shallowest of the three and its base appears higher in the root (Fig 6, a) than the base of the other two leaflets (l in Fig 7, a). Dense fibrous tissue does not form a circular investment of the entire aortic root at any of the levels described. This is especially true at the level of the leaflet bases.

## Discussion

The cyclic changes in the dimensions of the base of the aortic valve are similar to the changes in left ventricular geometry and volume in a normal cardiac cycle (Fig 2). The base perimeter is maximal in early systole. This coincides with rounding of the ventricular cavity known to occur during isovolumetric contraction.<sup>12</sup> The base perimeter decreases during systole. This coincides with the decrease in ventricular volume during systolic ejection. The perimeter is minimal at the end of systole. The perimeter increases during diastole. This coincides with the increase in the ventricular volume due to diastolic filling.

Although the changes of the base perimeter are similar to the known changes of left ventricular geometry and volume qualitatively throughout the normal cardiac cycle, a quantitative correlation between the base perimeter and the ventricular pressure in systole was not observed. This lack of quantitative correlation may be explained as follows. In systole, the behavior of the base is a combination of two factors: passive expansion (due to increased ventricular pressure) and active contraction (due to active tension in the base). Since these factors change in magnitude and relative proportion throughout systole, their effect on base behavior is constantly variable. For example, in Fig 3 one may see that in ectopic beat A the base contracts, whereas in ectopic beat B the base expands although ventricular pressure is increasing in both instances.

There is a quantitative correlation between the base perimeter and the ventricular pressure in diastole (Fig 4). The base of the aortic valve is relaxed and therefore expands passively in response to increasing ventricular diastolic pressure. This correlation is also indicated by the following observations. During both ectopic beats A and B (Fig 3) in which no blood was ejected (the leaflets did not open) the base perimeter was greater after the beats than before. The diastolic

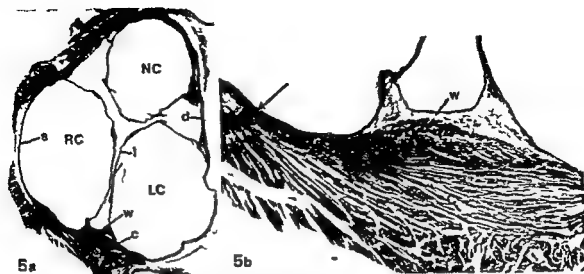


Fig 5 a Transverse section of aortic root approximately halfway between base at ventricle and sinus rims. Section shows three leaflets enclosing corresponding aortic sinuses and leaflet attachments to the wall. The root wall at this level consists of smooth muscle-elastic tissue (*a*) myocardium (*c*) or dense collagenous tissue (*d*) (Original magnification  $\times 25$ ) b Enlargement from 5 a of intervalvular trigonal region between right and left coronary leaflets. The root wall consists predominantly of circularly oriented myocardium, some fibers of which insert into the sinus wall (Original magnification  $\times 12$ )



Fig 6 a Transverse section of aortic root near base of noncoronary leaflet. At this level myocardium (*c*) makes up most of the wall tissue of two of the three trigonal regions and invests the wall of the right coronary sinus as well (Original magnification  $\times 3$ ) b Enlargement from 6 a of trigonal region between right and left leaflets. Masses of myocardium fill the space between walls of the two sinuses bounded internally by a very loose watery connective tissue (*u*) and an extremely thin intimal layer of denser tissue (*f*) curved onto the ventricular face of each leaflet. (Original magnification  $\times 10$ )

ventricular pressure and volume would also be expected to be greater after these abnormal beats than before.

Since the base of the aortic valve undergoes a consistent dimensional change during each normal cardiac cycle, it must participate in normal aortic

valve function. During opening of the aortic valve, expansion of the base to its maximum perimeter displaces the leaflet attachments outward. This change and the expansion of commissures observed in previous studies<sup>11</sup> would eliminate the zone of leaflet redundancy (Fig 8 A).



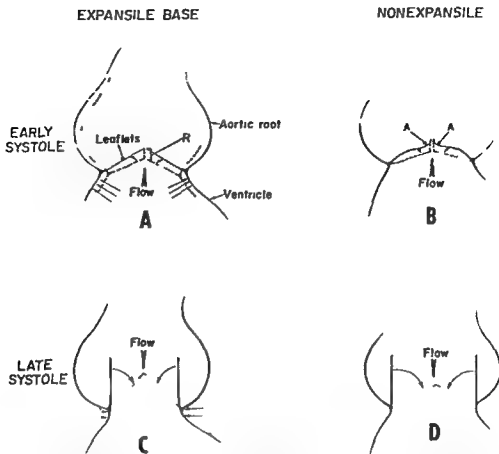
Fig 7 a Transverse section of aortic root at level of junction between ventricle and the two coronary leaflets of valve. Markers were placed at leaflet bases approximately at this level of the root (and somewhat more distally beneath the noncoronary leaflet which is more shallow and therefore was not cut by this section). Basal tissue of leaflets (*l*) consists of the same very loose watery connective tissue noted in previous figures. The myocardium which comprises the wall between the leaflet bases represents a distal extension of the interventricular septum (Original magnification  $\times 3$ ). b Enlargement from 7 a of the region between bases of the two coronary leaflets. Sectioning artifacts partially obscure the direction of constituent fibers but the dominant tissue is myocardium. Dense fibrous tissue (*d*) to the side of the left leaflet base (*l*) serves as the origin of one of the mitral valve leaflets (Original magnification  $\times 85$ ).

The entire leaflet can then move to the open position without bending in the radial direction. In the absence of expansion of the base as may occur with bioprostheses with nonexpansile sewing rings the load bearing portion of the leaflet would be displaced initially by the ventricular pressure creating increased bending at the line of coaptation (Fig 8 B). During closure of the normal aortic valve the contraction of the base to its minimum perimeter displaces the leaflets inward. This reduces the distance the leaflets must travel to close the valve (Fig 11 C) and also assures complete closure of the orifice. In the absence of contraction of the base (i.e. bioprostheses with a nonexpansile base) the valve closure may be delayed (Fig 11 D). In fact the closure may not occur until reversed flow is established. The leaflets would then have to arrest the momentum of the blood and this would produce additional stresses in the leaflets.

These results agree with those suggested by some investigators but differ from those observed by others. Swanson and Clark, using Silastic root casts of the aortic valve, observed a 10% change in the base diameter over a pressure

range of 20 to 120 mm Hg. Mercer<sup>4</sup> studied aortograms performed on humans and observed no change in the aortic valve annulus diameter. Zimmerman<sup>1</sup> and Reid, on observation of structure, speculated that the annulus does not change diameter. In contrast we have demonstrated that the base changes dimensions throughout the cardiac cycle in a manner similar to the changes in ventricular volume and the magnitude of change ranges from 5% to 28% over a wide range of systemic pressures (Table I).

The base of the aortic valve is capable of cyclic dimensional changes because it is partly composed of ventricular myocardium (Fig 7 a). At the base two of the three trigonal regions consist of myocardium and the right and left coronary leaflets and sinuses are encompassed by myocardium (Fig 6 a). Ventricular myocardium also forms part of the mitral valve annulus. Hinds and associates observed that the mitral valve annulus changed dimensions throughout the cardiac cycle. The dimensional changes of the mitral valve annulus reported by them are similar to those of the base of the aortic valve suggesting that similar forces are responsible for these changes. Since both the mitral valve and the



**Fig 8** A schematic presentation of the side view of the aortic valve. *A* Solid lines indicate expansive base and dotted lines indicate nonexpansile base. Expansion of the base (indicated by arrows in the ventricle) prior to the opening of the valve causes the leaflets to move from their old position (dotted lines) to their new position (solid lines). This eliminates the zone of leaflet redundancy (*R*). *B* In case of a nonexpansile base the increase in the ventricular pressure prior to the opening of the valve causes the leaflets to move from their old position (dotted lines) to their new position (solid lines) by a process of bending. This creates greater bending at the line of coaptation (indicated by *A*). *C* Contraction of the base (indicated by arrows in the ventricle) prior to the valve closure displaces the leaflets inward. This reduces the distance the leaflets have to travel to close (from solid lines to dotted lines). *D* In case of a noncontractile base the leaflets have to travel a larger distance. This may delay the valve closure.

aortic valve are attached to the ostium of the left ventricle. Changes in the dimensions of the ostium would produce similar changes in the aortic valve base and the mitral valve annulus.

These changes may be important in the design of valvular bioprostheses. If a bioprosthesis with a nonexpansile sewing ring is attached to the base of the aortic valve, cardiac contraction would produce shearing strain on the sutures and could cause suture breakdown or dehiscence producing a periprosthetic leak.

### Summary

The structure and behavior of the base of the aortic valve in the dogs were investigated. The

structure was studied under light microscopy to determine the distribution of collagenous elastic and myocardial elements. The dimensional changes were studied *in vivo* by attaching radio opaque markers to the base and observing their movement by x ray studies. The base is partly composed of ventricular myocardium. Two of the three trigonal regions consist of myocardium and the right and left coronary leaflets and sinuses are encompassed by ventricular myocardium. The collagenous tissue that lies internal to the myocardium is neither dense nor thick and does not form a complete ring. The cyclic dimensional changes in the base are similar to the cyclic changes in left ventricular geometry and volume.



The base perimeter is maximal in early systole coincident with the rounding of the ventricular cavity during isovolumetric contraction. The base perimeter decreases during systole when the ventricular volume decreases during systolic ejection. The base perimeter increases during diastole as the ventricular volume increases due to diastolic filling. The amount of cyclic change in the base perimeter at normal systemic pressure was different for different dogs. In four dogs the amount of change varied from 5% to 28% over a wide range of systemic pressures. The importance of the behavior of the base in normal valvular function is discussed. It is speculated that the mismatch between the nonexpansile sewing ring of an aortic bioprosthesis and the normally expansile base of the valve could cause occasional periprosthetic leaks.

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### Rupture of a papillary muscle of the tricuspid valve in primary pulmonary hypertension

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Rupture of a papillary muscle of the tricuspid valve (RPM TV) is rare and generally less dramatic than mitral papillary muscle rupture.<sup>1</sup> The usual causes of RPM TV are trauma, infective endocarditis, and myocardial infarction, occasionally cardiopulmonary resuscitation may also result in this complication. In all these circumstances there is direct damage to the papillary muscle and/or chordae which predisposes to or precipitates a rupture. To our knowledge spontaneous rupture of an otherwise normal papillary muscle of the tricuspid valve has not been reported in the English literature to date. We have recently studied a case of primary pulmonary hypertension (PPH) with spontaneous rupture of a tricuspid papillary muscle.

#### Case report

G P, a 70-year-old farmer, entered the hospital on November 1, 1977, with a 3-year history of dyspnea on effort. In March, 1977, while cycling he abruptly developed chest discomfort and breathlessness. He noticed for the first time a humming noise in his chest. This continued until the terminal event. His effort tolerance decreased rapidly, and he developed frequent episodes of paroxysmal nocturnal dyspnea (PND), rhytism, and swelling of the legs.

During the preceding 3 years he had experienced two episodes of arthralgia involving the knee joints accompanied by fever but no other joint was involved. There was no history of chest trauma, pain suggestive of myocardial infarction,

hemoptysis, venous thrombosis, surgical procedures, pulmonary embolism, or Raynaud's phenomenon. He had never stayed at high altitude or consumed weight-reducing drugs or any indigenous medicines. A family history of primary pulmonary hypertension was not obtained.

Clinical examination revealed a mildly jaundiced, poorly nourished man weighing 6 pounds. He was orthopneic and his extremities were cold and cyanotic. There was no evidence of thrombophlebitis, varicose veins, or edema. His pulse rate was 112/minute and regular with a low volume; blood pressure 97/60 mm Hg; respiratory rate 28/minute and oral temperature 37°C. Jugular venous pressure at 90 degrees was elevated up to the angle of the mandible and showed large C<sub>v</sub> waves. There was cardiomegaly with a hyperdynamic apical impulse in the fifth left intercostal space internal to the anterior axillary line. There was a moderate left parasternal lift with a systolic thrill felt all over the precordium but best felt along the lower left sternal border (LLSB). The first heart sound was normal and the second sound was obscured by a loud holosystolic murmur. A right ventricular gallop (S<sub>3</sub>) was present. A harsh S<sub>6</sub> holosystolic murmur was audible all over the precordium with maximum intensity at the LLSB but well heard at the apex and left axilla. There was no appreciable change in the intensity of the murmur with respiration or physical maneuvers. The lungs showed bilateral rales and the liver was enlarged and tender.

The total leukocyte count was 5500/mm<sup>3</sup> with a differential of 54% polymorphs, 42% lymphocytes, and 4% monocytes. Erythrocyte sedimentation rate was 3 mm/hour and hemoglobin 17.5 gm/100 ml with a hematocrit of 53%. Antistreptolysin O titer was 340 units; blood urea 24 mg/100 ml; serum bilirubin 3.2 mg/100 ml (direct reacting being 1.8 mg/100 ml); serum glutamic oxaloacetic transaminase 11 units. The scalar electrocardiogram (Fig. 1) showed a sinus tachycardia with a heart rate of 115/minute, right and left atrial enlargement, right ventricular hypertrophy with repolarization changes in right chest leads and clockwise rotation. The frontal plane QRS axis was +10 degrees.

An x-ray film of the chest (Fig. 2) showed a cardiothoracic ratio of 0.74, an enlarged right atrium, normal aortic shadow, and markedly enlarged pulmonary arteries, the right descend-

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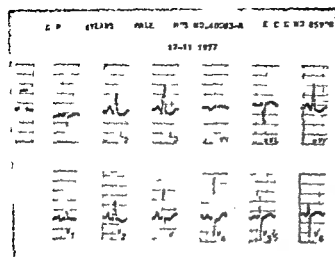


Fig 1 Electrocardiogram showing right and left atrial enlargement and right ventricular hypertrophy with clockwise rotation

ing branch measuring 22 mm in diameter. There was peripheral pruning of the pulmonary arteries. No left atrial enlargement could be made out by barium esophagram in the right anterior oblique (RAO) projection.

He slowly improved with conventional treatment and cardiac catheterization and selective cineangiography were carried out on the twenty-seventh hospital day under premedication with promethazine (2 mg intramuscularly) and phenobarbital (2 mg intramuscularly) with a provisional diagnosis of acute mitral regurgitation. Left ventriculography was done in the RAO projection followed by right ventricular and pulmonary arteriography. The patient later developed persistent hypotension and expired 23 hours after cardiac catheterization. A partial autopsy was obtained and heart, lungs and viscera were examined.

Hemodynamic data are detailed in Table 3 and Fig. 3 and 4. There was ventricularization of the right atrial tracing with rS waves. Right ventricular end-diastolic pressure (RV edp) was markedly elevated and the pulmonary artery pressures were near systemic level. The left ventricular end-diastolic pressure was normal. Cardiac index was low with systemic arterial desaturation.

A left ventricular angiogram showed marked regurgitation. A right ventricular angiogram showed marked enlargement of the right ventricle with severe tricuspid regurgitation and a large right atrium. A pulmonary arteriogram showed marked dilatation of the main pulmonary artery and its major branches with peripheral pruning. The wedge pressure in the pulmonary arteries.

At autopsy the heart weighed 135 g. The right atrium was markedly dilated and the right ventricle showed marked hypertrophy with a right ventricular free wall of 14 mm. The right ventricular free wall was 14 mm. The septal papillary muscle was ruptured at the chordal papillary muscle junction. The papillary muscles appeared normal on gross examination. The pulmonary valve measured 10 mm.

Table 1 Hemodynamic data

Site	Pressure (mm Hg)	Oxygen saturation (%)
Superior vena cava	—	45.0
Right atrium	CV 26 y 11 m 18	44.5
Right ventricle	82/0 16	44.5
Pulmonary artery	82/0 16 m 64	4.0
Left ventricle	101/0-6	
Aorta	101/0-6 m 11	50.0-55.0 mm
Cardiac index (L/min/m <sup>2</sup> )		
Pulmonary vascular resistance (dynes sec/cm <sup>5</sup> )		
Systemic vascular resistance (dynes sec/cm <sup>5</sup> )		

Abbreviations: CV and y denote respectively points on the atrial pressure curves; m = mean; LV edp = left ventricular end-diastolic pressure.

pulmonary artery and its major branches were dilated and showed arteriomatous lesions. There were no thrombi in the pulmonary arteries. The right atrium was normal and the mitral valve measured 2 cm. The left ventricular cavity was normal in size and the aortic valve measured 5.5 cm. The aorta was normal. Macroscopic examination of the liver and spleen showed evidence of marked chronic venous congestion.

The sections from the right ventricle showed evidence of hypertrophy of muscle fibers with focal areas of interstitial fibrosis. The ruptured papillary muscle showed no degenerative changes and appeared similar to other papillary muscles of the right ventricle showing patchy fibrosis. The lungs showed well marked evidence of pulmonary hypertension. There was widespread medial hypertrophy and intimal proliferation with many pleiform (Fig. 6 A) and dilated (Fig. 6 B) lesions.

## Discussion

Rupture of a papillary muscle is a relatively rare cardiac lesion. In the vast majority of cases it occurs on the left side as a complication of acute myocardial infarction. Little is known of the real incidence, etiology and natural history of rupture of papillary muscle of the tricuspid valve. The condition was first clinically diagnosed by Parmley and associates in 1938 in a patient with nonpenetrating trauma to the chest. In 1977 Gerry and colleagues could collect only nine cases of RPM TV from the English literature to which they added two of their own. The relative scarcity of reported cases of RPM TV in comparison to the left side may be at least in part due to the less dramatic clinical presentation and the difficulties in establishing a firm diagnosis in the former.



Fig 2 A Posteroanterior chest radiograph. Note marked dilatation of the right atrium and the proximal pulmonary arteries B Esophagram in right anterior oblique projection showing no evidence of left atrial enlargement

In 7 out of the 11 reported cases RPM TV resulted from trauma to the chest it followed infective endocarditis in three cases and myocardial infarction in one This is in sharp contrast to left sided RPM which in the majority of patients results from acute myocardial infarction Although there are reports of acute tricuspid regurgitation following myocardial infarction RPM TV has been confirmed only in one case to date While spontaneous rupture of an other wise normal papillary muscle is known to occur on the left side we are unaware of any reported instance of such an occurrence on the right side

In our patient who had PPH the RPM TV occurred spontaneously Gerry and associates point out that the increased wall tension in a dilated ventricle leads to increased tension in papillary muscles and chordae tendinae and thus predisposes to their rupture and in the present case RPM TV occurred during cycling Interestingly in this case the ruptured and unruptured papillary muscles on the right side showed no significant histologic differences and the rupture was at the chordopapillary junction unlike those associated with acute myocardial infarction or trauma

Primary pulmonary hypertension is not an uncommon clinical entity in India A report of 91 cases of pulmonary hypertension has been recent

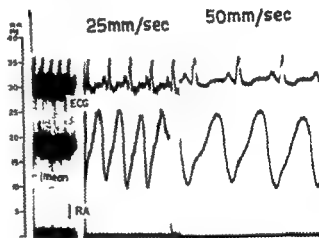


Fig 3 Right atrial pressure tracings showing ventricularization

ly presented from this center and unexplained PND was present in 10% Although the pathogenesis is not clear PND has been reported in patients with isolated tricuspid insufficiency As the pulmonary lymphatics empty into the systemic veins any sudden elevation of the central venous pressure could impede pulmonary lymphatic drainage resulting in pulmonary congestion Unley and associates have demonstrated by well-designed experiments the importance of pulmonary lymphatics in the causation of pulmonary edema A reversed Bernheim

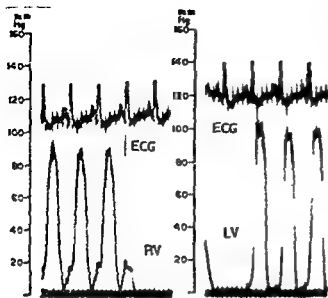


Fig 4 Right and left ventricular pressure (RV and LV) tracings. Note near systemic right ventricular pressures.



Fig 6 Histopathologic sections of the lung. A Plexiform lesion B Dilatation lesion. (Hematoxylin-eosin stain magnification  $\times 160$ )

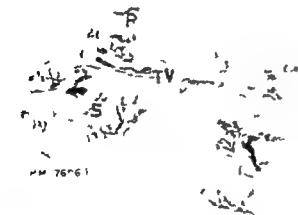


Fig 5 The right ventricle (RV) and the right atrium (RA) have been opened to display the tricuspid valve (TV) and papillary muscles. Arrow points to the ruptured septal (S) papillary muscle.

effect was ruled out by the normal LV edp

The physical signs of isolated tricuspid regurgitation in patients with normal right ventricular pressures are pathognomonic. However the respiratory variation of the murmur may be difficult to appreciate in a case of severe right ventricular hypertension with a very loud murmur (Grade 5 or 6). A Valsalva maneuver may not show significant changes as noted in the present case.

Electrocardiograms may be misleading in some cases of RPM TV. A review of the available electrocardiograms of patients reported to have

isolated tricuspid insufficiency by Morgan and Forker showed criteria for left atrial enlargement in about 25% while right atrial enlargement was observed in only one case out of 15. Our case showed features of left and right atrial enlargement. These findings along with the history of PND led us to the initial mistaken clinical diagnosis of acute mitral regurgitation. Occasionally the chest x ray film may appear normal in non-intensive tricuspid regurgitation.

It is often said that the hemodynamic consequences of severe tricuspid regurgitation can be well tolerated for long periods.<sup>11,12</sup> Robin and associates<sup>13</sup> have demonstrated long survival of several patients after total removal of the tricuspid valve without prosthetic replacement. At least two authors have emphasized that RV edp would be normal or only slightly elevated.<sup>1,14</sup>

The hemodynamic changes and the natural history of acute tricuspid regurgitation would also be influenced by the underlying cardiac condition. Nearly 50% of patients with RPM TV are dead within 2 weeks and all are either dead or had surgery within 4 months'. Our patient lived for 9 months after RPM TV.

# Summary

Rupture of a papillary muscle of the tricuspid valve is a rare occurrence and nontraumatic rupture is still rarer. We describe a 26 year old male with primary pulmonary hypertension presenting with severe dyspnea and paroxysmal nocturnal dyspnea following spontaneous rupture of the septal papillary muscle of the tricuspid valve. The clinical diagnosis was confirmed at autopsy.

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# Bjork-Shiley mitral valvular dehiscence\*

Documented by radiography echocardiography fluoroscopy and cineangiography

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Radiography echocardiography fluoroscopy and cineangiography are non invasive ways to evaluate dysfunction of prosthetic valves. The normal echocardiographic appearance of a Bjork Shiley prosthetic valve has been reported. Furthermore two cases with echocardiographic features of Bjork Shiley mitral perivalvular leaks have been reported. However only one of these cases had cineangiographic confirmation. We report here a case with combined radiographic echocardiographic fluoroscopic as well as cineangiographic findings of prosthetic valvular dehiscence confirmed at surgery.

## Case report

The patient was a 20 year old black male. He presented on September 1 1977 with a three week history of an illness characterized by fever malaise as well as left wrist and right ankle pain. He had been treated with oral penicillin prior to his presentation. He denied any venereal contact dysuria or pyuria recently. He denied further any history of drug abuse heart murmur prior heart disease or rheumatic fever. He was admitted to the hospital where physical examination revealed a temperature of 102.4 degrees mild dehydration associated with heat swelling and decreased range of motion of the left wrist and right ankle. Erythematous lesions at the palms and soles

were noted. No abnormal cardiovascular findings were noted. The patient was felt to have partially treated disseminated gonococcal septicemia. He was given high doses of intravenous penicillin with continued temperature spikes. However on September 3 1977 the blood joint fluid and urine samples were growing *Staphylococcus aureus* and the antibiotic was changed to methicillin. Re examination revealed a new systolic murmur which was initially thought to be benign. However over the next 3 days the murmur increased in intensity and was felt to be consistent with mitral insufficiency. An S sound developed as well. An echocardiogram was performed and revealed a normal size left ventricle as well as an enlarged left atrium. Vegetations on the mitral valve were also demonstrated.

On September 8 1977 a left central facial paresis was noted. A cerebral angiogram revealed an obstruction in the right internal carotid artery age undetermined. On September 1 the patient was noted to have an absent right brachial pulse. An angiogram revealed obstruction at the axillary brachial region and circumflex-humeral level. Embolectomy was performed with a purulent embolus removed. He was treated with vancomycin with defervescence of his fever in three days. He remained afebrile until September 29 when he again began to spike daily temperatures. All blood cultures including fungal cultures were negative to date.

On October 7 1977 the patient underwent right heart catheterization (Table I A). Pulmonary artery pressures were essentially normal. Pulmonary capillary wedge pressures showed an A wave of 8 mm Hg and V wave of 11 mm Hg with a mean of 11 mm Hg. There was no evidence of a left to right shunt. Oxygen saturation studies were normal. The cardiac index was noted to be 3.6 liters per minute per square meter determined by thermodilution technique. Left ventricular angiogram revealed 2+ mitral regurgitation. There was also the finding of a pedunculated abnormality of the anterior mitral leaflet suggestive of a vegetation. The left ventricular end diastolic pressure was 8 mm Hg at rest and 10 mm Hg post angiography. There was no evidence of aortic regurgitation.

On October 8 1977 the patient underwent mitral valve

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Fig 1 Chest x ray revealing a markedly tilted valve and florid pulmonary edema

Table 1 Cardiac catheterization data Mean systolic and diastolic pressures (mm Hg)

Location	Date of procedure			
	A Oct 7 77	B Oct 21 77	C Nov 29 77	D Dec 11 77
Right atrium	a = 6 v = 5	a = 8 v = 6	a = 8 v = 4	—
Right ventricle	37/6	28/6	50/10	—
Pulmonary artery	32/8	26/12	50/30	40/24
Pulmonary capillary wedge	22	20	40	28
Pulmonary capillary wedge	a = 8 v = 11	a = 14 v = 18	a = 22 v = 40	a = 36 v = 40
Left ventricular end diastolic pressure	8	14	28	16
Cardiac index (L/min/M <sup>2</sup> )	3.6	—	—	—

replacement with a No 27 Hancock porcine valve. A 2 by 2 cm vegetation was seen on the atrial side of the anterior leaflet of the mitral valve. Several small crust like lesions were also located on the mitral valve near the anteromedial commissure. Postoperatively the patient developed first degree A-V block, a pericardial effusion and right peroneal nerve damage.

He remained stable until October 21, 1977, when he was found to be in acute pulmonary edema. Cardiac catheterization (Table 1, B) revealed a trace amount of mitral regurgitation with normal left and right sided pressures. He was treated with diuretics with significant clinical improvement. However, on repeated examination the patient was found to

have physical findings compatible with that of moderate to severe mitral stenosis with progressive pulmonary hypertension secondary to a small annular ring which would only accommodate a No 27 Hancock valve. The patient therefore underwent recatheterization on November 22, 1977 (Table 1, C). Pressures were noted to be as follows: a pulmonary artery pressure of 50/30 mm Hg with a mean of 40 mm Hg and a pulmonary artery wedge pressure with an A wave of 22 mm Hg and a V wave of 40 mm Hg with a mean of 28 mm Hg. In light of the progressive rise in pulmonary artery pressures, the patient underwent mitral valve replacement on November 30, 1977 with a No 27 Bjork Shiley prosthetic valve. The patient did well postoperatively.



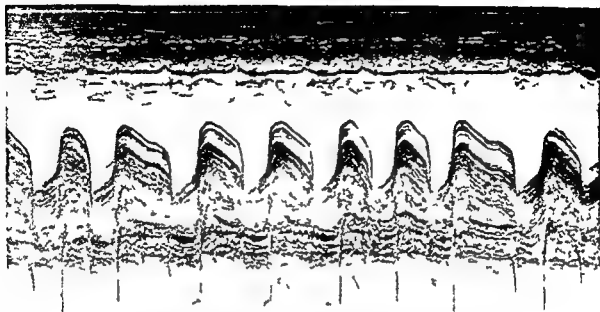


Fig 2 Echocardiogram with a characteristic hump on the anterior leaflet of the mitral valve consistent with frank dehiscence

On the morning of December 11 1977 the patient had acute onset of dyspnea tachycardia and hypotension Physical examination revealed him to be lethargic confused and in shock with rales over the entire lung fields Cardiac examination revealed crisp closing prosthetic clicks There were no murmurs noted His chest x ray revealed a markedly tilted valve and florid pulmonary edema (Fig 1) An electrocardiogram revealed the patient to have a left bundle branch block and first degree heart block unchanged from previous tracings The patient rapidly deteriorated necessitating intubation vasopressors and other measures—i.e large doses of furosemide steroids and chest tubes placed bilaterally for drainage A Swan Ganz catheter was inserted and revealed a pulmonary artery diastolic pressure of 36 mm Hg

Emergency portable echocardiogram was performed and revealed a characteristic hump on the prosthetic valve echo consistent with frank dehiscence of the prosthetic valve (Fig 2) He was taken to the cardiac catheterization laboratory (Table 1 D) where the pulmonary capillary wedge mean pressure was 30 mm Hg with an A wave of 36 mm Hg and a V wave of 40 mm Hg The pulmonary artery pressure was 40/24 mm Hg with a mean of 28 mm Hg The left ventricular end-diastolic pressure was 16 mm Hg Cardiac index was determined to be 1.1 L/min/M<sup>2</sup> by thermodilution technique Fluoroscopy revealed marked tilting of the prosthetic valve with an excursion of 51 degrees suggestive of dehiscence of the prosthesis (Fig 3) A left ventricular angiogram revealed 4+ mitral regurgitation (Fig 4) The patient was immediately taken to surgery where the valve in the annulus was noted to be supported by only three sutures while the other 10 sutures had pulled through The valve was also noted to be prolapsing into the left atrium The valve was removed and was replaced

with a new No 27 Bjork Shiley mitral valve Postoperatively the patient became septic and died on January 7 1978

## Discussion

Evaluation of prosthetic valve function requires strict attention to detail and frequent serial examinations Changes on auscultation x rays echocardiography and other non invasive examinations are evident only with repeated evaluation Valvular dysfunction may vary from obstruction to frank valvular dehiscence and massive regurgitation as in our patient The dehiscence of the sewing ring due to suture breakage or disruption from the sewing bed because of friable calcific or necrotic tissue is a major cause of dysfunction It is helpful to be familiar with the particular valve and its difficulties in order to arrive at an expeditious diagnosis of the nature of the malfunction This patient presented with a sudden calamity The mode and time of presentation of his valvular dysfunction was a major aid in arriving at the diagnosis During his dramatic deterioration the patient manifested normal prosthetic sounds and the absence of a murmur in spite of severe paravalvular leakage

The x ray revealed the patient to be in florid pulmonary edema and to have exaggerated tilting



Fig 3 A and B Fluoroscopic documentation of marked tilt<sup>o</sup> of the valve with an excursion of 51 degrees suggesting dehiscence

of his valve. Cinefluoroscopy was valuable in detecting excessive cyclic excursion of the sewing ring strongly suggestive of valvular dehiscence. 4+ mitral regurgitation was noted around the sewing ring.

The detachment of the valve prosthesis is caused by the breaking and loosening of sutures from the sewing bed. This was brought about probably by the strain in the sutures in the anchoring tissue resulting from the force of the ventricular contraction. In the mitral position the normal movement of the prosthesis is anterior and posterior along its long axis and side to side on its vertical axis. The strain on the suture line is greatest at the medial and lateral aspects of the sewing ring. If the suture breaks in one of these locations as in our patient it puts a strain on the adjacent sutures causing progressive dehiscence and may lead to complete detachment and embolization of the entire prosthetic valve.

The prosthetic detachment was diagnosed unequivocally by roentgenographic techniques. Plain x ray of the chest suggested detachment by the abnormal orientation of the prosthesis. The detachment was more evident by fluoroscopy. A to and fro motion of the partially detached valve was seen and the axis at the base of the prosthesis changed during ventricular contraction and relaxation. Cinefluoroscopy permitted easy measurement of this tilting motion. The foregoing constituted a positive method of demonstrating the prosthetic valve detachment.

Studies using the echocardiogram in the diagnosis of prosthetic valve dysfunction are now



Fig 4 A left ventricular angiogram revealing 4+ mitral regurgitation

becoming more frequent. Correlation of the echocardiogram with radiography, fluoroscopy and angiography have defined the movement patterns for normally functioning prosthetic valves. Other reports have shown malfunction characterized by disc motion, disc excursion and relation of the disc and cage motions to other cardiac events. In particular, disc motion of the Bjork Shiley prosthetic valve can be readily assessed by echocardiography. Because of the asymmetry of the valve, proper disc and echo transducer alignment are necessary for optimal detection of disc excursion. According to Douglas and Williams,<sup>1</sup> when the ultrasound beam is perpendicular to the maximally open disc, such an alignment usually is most readily achieved. Patients who undergo

prosthetic valve replacement should have an initial prosthetic echogram accomplished postoperatively as soon as technically feasible

Although contrast angiography is the most sensitive indicator of prosthetic valvular detachment radiography echocardiography fluoroscopy and cineradiography should be used in all suspected cases. Serial studies with the foregoing non invasive procedures beginning with an early postoperative control study are recommended

### Summary

This case report presents combined radiographic echocardiographic fluoroscopic and cineradiographic findings of the dehiscence of a Bjork Shiley mitral prosthetic valve. The valvular dehiscence was confirmed at surgery. A distinct rounding of the opening phase of the valve was recorded on the echocardiogram. Other clinical evidence documenting the severe valvular dehiscence is reported in detail. Non invasive procedures are therefore invaluable in recording prosthetic valvular dysfunction.

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## Left and right ventricular myocardial infarction in idiopathic dilated cardiomyopathy

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**DR ROBERTS:** Dr Isner will present the *patient's story and clinical findings*.

**DR ISNER:** N S (Washington Adventist Hospital No. 144031) was a 62-year-old woman who died on September 23, 1978. Since age 53 years (1969) she had known of a heart murmur and a large heart. She was asymptomatic until age 60 years when she developed exertional dyspnea and pedal edema. Examination then revealed distended neck veins, basilar pulmonary rales, a large heart, S and S sounds, an apical holosystolic murmur, and another systolic murmur which increased with inspiration at the left sternal border. The liver was palpable and both legs were edematous. Electrocardiogram disclosed sinus tachycardia with non-specific ST-T wave changes. The patient was started on digoxin and diuretics. She was hospitalized twice during the subsequent 2 years for overt congestive heart failure. Ten months before death an echocardiogram disclosed a dilated poorly contracting left ventricle.

Because of increasing congestive cardiac failure she was hospitalized 5 days before death. She denied ever having chest pain. She had drunk alcohol infrequently and never had hypertension to her knowledge. Her blood pressure on admission was 110/90 mm Hg with a pulsus paradoxus of 20 mm Hg. Despite distention above the sternal angle of the neck, veins, the lung fields

were clear. The right ventricular impulse was more prominent than the left ventricular impulse. The remainder of the precordial examination was unchanged from the findings described 2 years earlier. The liver was enlarged and severe (4+/4+) subcutaneous edema was present in the lower legs. The hematocrit was 35 per cent, fasting serum glucose 109 mg/dl, serum total cholesterol 170 mg/dl, serum glutamic oxaloacetic transaminase 61 mU/ml (normal 7 to 40), lactic dehydrogenase 302 mU/ml (normal 100 to 220), creatinine phosphokinase 208 mU/ml (normal <145) with cardiac (MB) fraction 1.9 (nl  $\leq$  3 per cent). The electrocardiogram (Fig. 1) showed a vertical axis and inverted T waves in Leads III and aV, the chest radiograph (Fig. 2) showed marked cardiomegaly, and the echocardiogram (Fig. 3) was similar to the one recorded 10 months earlier. Her course worsened. On the day of death her skin cooled and became moist, the blood pressure fell, and the electrocardiogram (Fig. 1) showed left bundle branch block. With ambu bag pulmonary assistance the arterial pO<sub>2</sub> was 69 mm Hg, pCO<sub>2</sub> 55 mm Hg, and pH 7.12. (On admission when breathing room air the pO<sub>2</sub> had been 85 mm Hg, pCO<sub>2</sub> 31 mm Hg, and pH 7.45.) The patient was intubated and a Swan-Ganz catheter was inserted. Initial pressures (in mm Hg) were right atrial mean 24, right ventricle 55/24, pulmonary artery 55/30, and mean pulmonary capillary wedge 25. Despite intravenous administration of saline and dopamine the systemic blood pressure continued to fall. Subphoid insertion of a needle ruled out cardiac tamponade. Shortly thereafter fatal ventricular fibrillation occurred.

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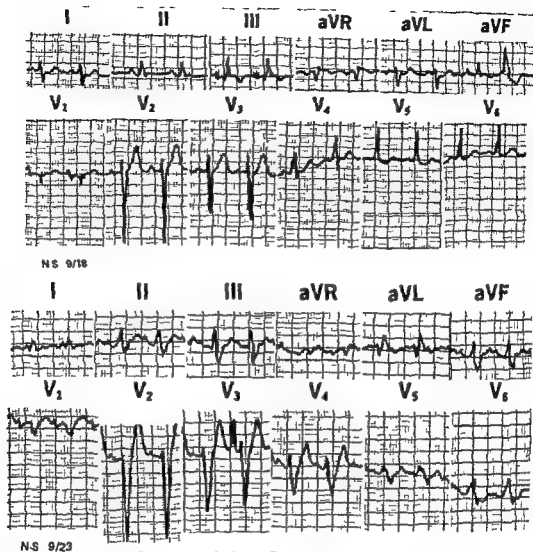


Fig 1 Electrocardiograms. On admission (9/18) 5 days before death, the T wave inversions in Leads III and aV are the only findings consistent with a scar in the posterior left ventricular free wall. Left bundle branch block appeared on the day of death (9/23).

DR ROBERTS: Dr Virmani, would you describe the findings at necropsy?

DR VIRMANI: At necropsy (WAH No A7867) about 100 ml of serous fluid was present in the pericardial sac. The heart weighed 580 grams. All four chambers were markedly dilated. There was transmural scarring of the posterior walls of both left and right ventricles and of the adjacent ventricular septum (Figs 4 and 5). There were no foci of myocardial necrosis. Thrombi were present in both ventricles and in the right atrial appendage. The major epicardial coronary arteries were wide open (Fig 6). At no point were any portions of any epicardial coronary artery >25 per cent narrowed in cross sectional area. The lungs together weighed 900 grams. Two hemorrhagic

infarcts were present: one in the lower lobe of the left lung and the other in the upper lobe of the right lung. Some adjacent pulmonary arteries contained thromboemboli. Small healed infarcts were present in each kidney. The liver weighed 1450 grams and was congested.

DR ROBERTS: Thus we have a patient who was known to have cardiomegaly and an abnormal electrocardiogram for at least 10 years, evidence of chronic congestive heart failure for at least 2 years, never evidence of chest pain and at necropsy, very dilated ventricular cavities containing thrombi, large transmural scars involving the free walls of both left and right ventricles and the ventricular septum and widely patent, virtually normal epicardial coronary arteries. Dr

Itscowitz what was your *clinical diagnosis* in this patient?

DR ITSCOWITZ Three possibilities were considered. One was coronary heart disease particularly in view of her age (62 years). Against this diagnosis however was the absence of chest pain, electrocardiographic absence of clear myocardial damage and the absence of risk factors for atherosclerosis. Her total serum cholesterol was 170 mg/dl, she did not smoke, her blood pressure had always been normal and her fasting blood sugar was normal. Idiopathic dilated cardiomyopathy was favored by the history of chronic congestive heart failure, the marked cardiomegaly and the absence of chest pain or clear evidence of organic valve disease. The third diagnosis considered was pericardial heart disease. This possibility was considered because of the extremely large cardiac silhouette by chest radiograph, the extreme prominence of features of right-sided congestive failure (the neck veins were enormously distended while the lung fields were clear and she was able to lie flat in bed without distress) and the occurrence of diastolic pressures in the right ventricle and main pulmonary arteries similar to the mean pressures in the right atrium and pulmonary arterial wedge position. The possibility of cardiac tamponade was so high immediately before death that a needle was inserted into the pericardial sac but fluid was not detected.

DR ROBERTS Dr Virmani, your necropsy observations in this patient are consistent with idiopathic dilated cardiomyopathy. What morphologic criteria make this diagnosis at necropsy?

DR VIRMANI To diagnose idiopathic dilated cardiomyopathy at necropsy, five criteria must be met: (1) both ventricular cavities must be dilated; (2) the heart weight must be increased ( $> 350$  gms in adult women and  $> 400$  gms in adult men); (3) the lumens of the major epicardial coronary arteries must be  $< 75$  per cent narrowed in cross-sectional area by atherosclerotic plaque; (4) the four cardiac valves must be anatomically normal or have only minimal focal small scars; and (5) no associated systemic or other known cardiovascular conditions can be present. In addition, intracardiac thrombi are usually present in one or more cardiac cavities, but this finding is not essential for diagnosis.

DR ROBERTS Dr Itscowitz, although many clinical definitions of idiopathic dilated cardio-



Fig. 2 Posteroanterior chest radiograph on admission 5 days before death. The cardiac silhouette is markedly enlarged and the pulmonary vessels are prominent—i.e. "congested."

myopathy include the absence of systemic hypertension and the absence of valvular heart disease. Many of these patients have systemic hypertension and most before the end have one or more precordial murmurs. How do you diagnose idiopathic dilated cardiomyopathy in the presence of systemic hypertension or precordial murmurs or both?

DR ITSCOWITZ If systemic hypertension is present throughout the entire clinical course, I do not believe the diagnosis of idiopathic dilated cardiomyopathy would then be appropriate. If systemic hypertension were present however only at the beginning of the patient's course and was absent in the last few months, the diagnosis of idiopathic dilated cardiomyopathy could still be proper. In other words, if the blood pressure rises progressively and persists throughout the course, diagnosis of idiopathic dilated cardiomyopathy would not be appropriate.

In general, precordial murmurs appear relatively late in the course and the murmurs may get louder as the ventricular cavities get bigger. In the present patient, however, a precordial murmur preceded the presence of overt congestive heart failure, but that is unusual.

DR ROBERTS An unusual feature of this

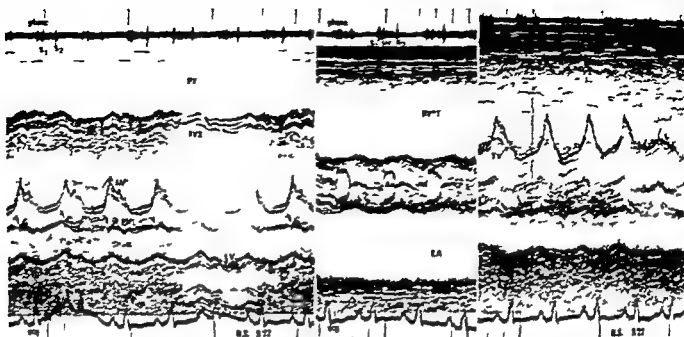


Fig 3 Echophonocardiograms recorded one day before death. Left ventricular dilatation with diminished excursion of both septum (LVS) and left ventricular (LV) free wall. There is no evidence of pericardial effusion. P1 = right ventricle AVL and PVL = anterior and posterior mitral leaflets respectively. Middle Severe dilated right ventricular outflow tract (RVOT). Ao = aortic valve within aorta. LA = left atrium. SV = mitral valve. Right Another view of the markedly dilated right ventricle at the level of the tricuspid valve (TV).

patient morphologically was the presence of a very large cardiac scar involving not only the left ventricular free wall and ventricular septum but also the right ventricular free wall. I have studied the hearts of 153 necropsy patients with idiopathic dilated cardiomyopathy and this patient had the largest ventricular scar of any. In addition this is one of the few patients with idiopathic dilated cardiomyopathy seen personally at necropsy with extensive right ventricular scarring. Dr Virmani could you enlighten us to the cause of ventricular scarring in patients with idiopathic dilated cardiomyopathy?

DR. VIRMANI: The cause of cardiac ventricular scarring in patients with idiopathic dilated cardiomyopathy is unclear. By definition the epicardial coronary arteries cannot be significantly narrowed in this condition and therefore narrowing of these vessels is not a cause of the scarring. Embolism to the coronary arteries from thrombi located within the left side of the heart is a potential cause of left ventricular scarring. In patients with coronary embolism however whom we have studied at necropsy there usually is evidence of occlusion of one or more of the

intramural coronary arteries. Multiple histologic sections of the ventricular walls in the present patient however disclosed no abnormality of the intramural coronary arteries and that observation is strong evidence against embolism as a cause of scarring. The extremely diminished cardiac output which occurs in patients with idiopathic dilated cardiomyopathy generally leads to a "global" myocardial ischemia and not so much to a focal myocardial ischemia. Ventricular scarring is always focal and therefore its explanation in these patients is uncertain.

DR. ROBERTS: Recently Dr Isner and I reviewed a large number of necropsy patients with coronary heart disease who had both right ventricular and left ventricular myocardial infarction. The present patient however has that right ventricular infarction may occur in the absence of coronary arterial luminal narrowing. Dr Isner what features allow the clinical diagnosis of right ventricular infarction?

DR. ISNER: From review of clinical and necropsy features of 33 patients with right ventricular myocardial infarction associated with left ventricular infarction three findings suggest clinical

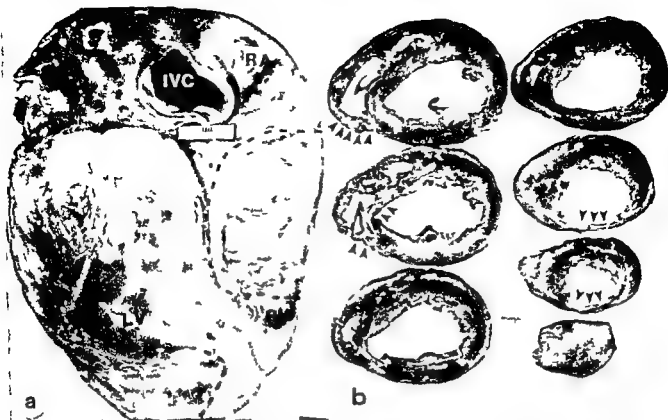


Fig 4 a and b Transmural ventricular scarring in the patient described ■ Posterior view of heart showing external appearance of left ventricular (LV) and right ventricular (RV) scars (enclosed by dashed lines) b Transverse sections of ventricles from base (upper left) to apex (lower right) The arrows designate sites of transmural scarring LA = left atrium RA = right atrium IVC = inferior vena cava

ly the presence of right ventricular infarction (1) electrocardiographic evidence of an inferior or posterior left ventricular wall myocardial infarction (2) evidence of right ventricular dilatation and (3) a right ventricular filling pressure equal to or out of proportion to the left ventricular filling pressure Of our 33 patients all had an associated infarction of the posterior ( inferior ) wall of the left ventricle In contrast of 97 patients with isolated anterior wall infarction of the left ventricle none had associated right ventricular myocardial infarction Furthermore among the patients with posterior wall left ventricular infarcts those with right ventricular myocardial infarcts had right ventricular dilatation observed at necropsy nearly three times more frequently than did the patients without right ventricular myocardial infarcts Comparison of patients with right ventricular myocardial infarction however disclosed no differences in the patients age sex

extent of coronary arterial luminal narrowing presence of right ventricular hypertrophy or right ventricular thrombi or the length of symptoms of myocardial ischemia

DR ROBERTS Dr Isner *what clinical features in the present patient in retrospect might have suggested the presence of healed right ventricular infarction?*

DR ISNER First as Dr Itscowitz pointed out the signs of right ventricular failure were out of proportion to those of left ventricular failure The neck veins were severely distended and yet the patient could lie flat in bed without respiratory distress Secondly echocardiograms done at 10 months and at one day before death both demonstrated severe right ventricular dilatation ■ finding at least consistent with right ventricular myocardial infarction Surprisingly no electrocardiographic evidence of unequivocal infarction of the posterior wall of the left ventricle however



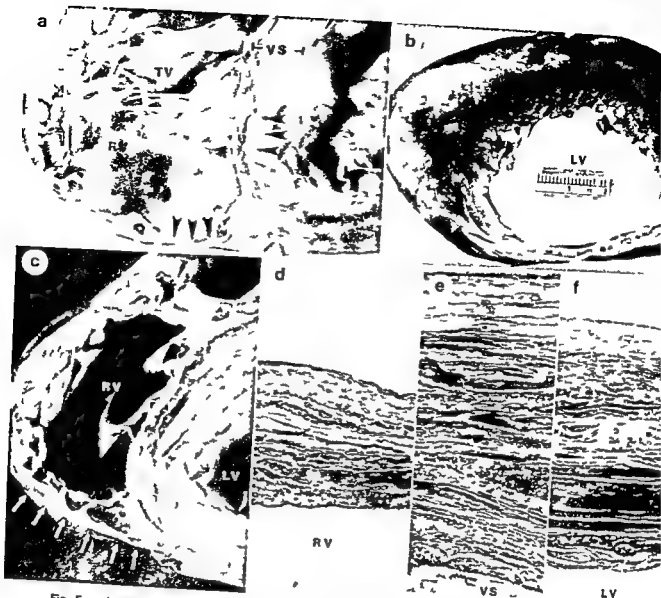


Fig 5 a through f Transmural ventricular scarring a Arrows designate thinning due to healed myocardial infarct of ventricular septum (VS) and posterior wall of ventricle (RV) TV = tricuspid valve b Posterior wall of left ventricle (LV) which is scarred and thinned. c Posterior right ventricular scar (arrows) at level approximately 1 cm caudal to a d e f Photomicrographs of healed transmural infarcts of RV VS and LV respectively (Movat stains each original magnification  $\times 36$ )

was present. The elevation of the pulmonary arterial diastolic pressure to a level of 9 mm Hg greater than the mean pulmonary capillary "wedge" pressure was a reflection of pulmonary arterial hypertension in this patient, the result of pulmonary emboli. The elevation of right ventricular end-diastolic pressure, however, was out of proportion to both the elevated left ventricular end-diastolic pressure and the degree of pulmonary hypertension resulting from the pulmonary emboli. The degree of elevation of right ventricular end-diastolic pressure in this patient would be

consistent with an associated right ventricular myocardial infarction.

**DR. ROBERTS:** Dr. Isner, you and others have mentioned that the signs of right ventricular infarction may mimic those of cardiac constriction or cardiac tamponade. How do you distinguish the signs emanating from right ventricular infarction from those of pericardial heart disease?

**DR. ISNER:** First, electrocardiographic or enzymatic evidence of myocardial infarction certainly would increase suspicion of an associated right

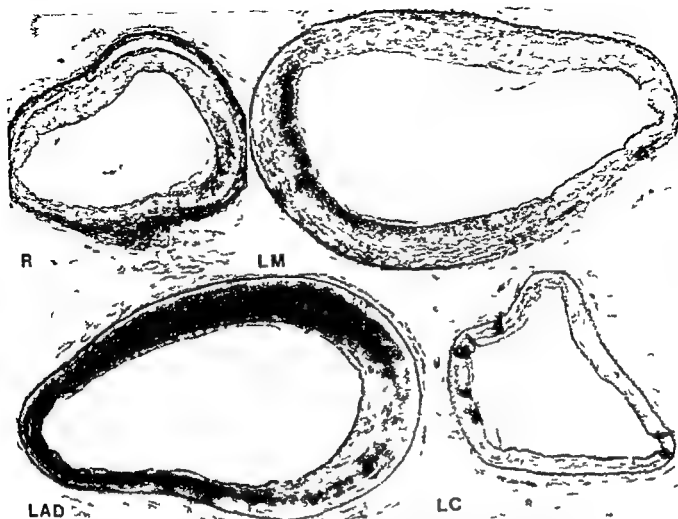


Fig 1 Photomicrographs of each of the four major (right [R], left main [LM], left anterior descending [LAD], and left circumflex [LC]) coronary arteries at sites of maximal luminal narrowing. None of the coronary arteries were narrowed  $> 20$  per cent in cross sectional area (Movat stain; each original magnification  $\times 24$ )

ventricular infarction as opposed to primary pericardial disease. Secondly, right ventricular dilatation would be most unusual in a patient with impaired cardiac filling due to pericardial heart disease whereas right ventricular dilatation is commonly present in patients with right ventricular myocardial infarcts. Finally, differentiation between pericardial heart disease and right ventricular myocardial infarction may not be possible on the basis of physical examination alone and the use of noninvasive tools such as echocardiography and radionuclide angiography or invasive studies may be necessary to determine whether the clinical appearance of the patient is due to pericardial heart disease or to right

ventricular myocardial infarction associated with left ventricular infarction.

**DR. ROBERTS:** The majority of patients with idiopathic dilated cardiomyopathy have mural thrombi in one or more ventricular cavities. The most frequent site is the left ventricle, next the right ventricle, third the right atrial appendage, and fourth the left atrial appendage. The exact cause of these intracardiac thrombi is unclear but it seems most reasonable to believe that they result simply from relative blood stasis or inadequate chamber emptying. The danger of intracardiac thrombi obviously is that they are sources of systemic and pulmonary emboli. In the present patient emboli were observed at necropsy in both

renal and pulmonary arteries with resulting infarcts of each organ. Dr Isner in retrospect *what features suggested pulmonary embolism as the terminal event in our patient?*

DR ISNER: The acute drop in blood pressure in spite of longstanding congestive heart failure, the drop in systemic arterial oxygen content, and the appearance of left bundle branch block suggested this possibility.

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## Prevention of cardiogenic shock

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Cardiogenic shock occurs in 10% to 15% of hospitalized patients with acute myocardial infarction. It is usually related to massive destruction of the myocardium. In a few patients the direct cause is a sudden structural catastrophe such as papillary muscle rupture or septal perforation. Among those who die from cardiogenic shock the amount of left ventricular myocardium infarcted varies from 35% to 70%.<sup>1</sup>

Since shock is associated with massive myocardial infarction therapeutic interventions have been unrewarding despite intra aortic balloon counter pulsation and coronary revascularization with or without additional surgery.

That appropriate early intervention might limit myocardial damage and prevent cardiogenic shock was suggested nearly 10 years ago. It was found that when therapy was initiated within 3 hours of the onset of myocardial infarction the incidence of cardiogenic shock was 4% and when therapy was delayed longer than 3 hours the incidence was 13%.

Extensive loss of myocardium responsible for cardiogenic shock occurs in a stepwise fashion.<sup>1,2</sup> Extension of recent infarction occurs in close temporal proximity to the clinical onset of shock.

It has been observed that every patient dying with cardiogenic shock had damage to the ventricular apex and that 84% of such patients had severe disease of the left anterior descending coronary artery. It is of interest that patients

dying from left ventricular failure following myocardial infarction show extensive myocardial damage similar to that of patients dying from cardiogenic shock.<sup>3</sup>

### Pathogenesis of extension of infarction

That the ultimate magnitude of the infarct may be influenced by factors operating after coronary occlusion has been confirmed in the animal laboratory. Clinical evidence supports the proposition that progressive myocardial damage may occur in patients who later develop shock.<sup>4</sup> Progressive destruction of myocardium following coronary occlusion is readily explicable. Dysrhythmias and autonomic disturbance immediately after the onset of coronary occlusion may alter unfavorably the balance between oxygen supply and demand at the periphery of the infarct. Aggravation of left ventricular dysfunction is likely to result. This predisposes to an increase in left ventricular filling pressure or a reduction in arterial pressure or both. There may be a compensatory increase in heart rate. Any combination of these changes will have further detrimental effects on jeopardized myocardium. Thus there may be a vicious cycle involving continuing extension of the infarct and impairment of left ventricular function.

In the prevention of progressive myocardial damage the time at which therapy is initiated is crucial. In the dog irrecoverable damage to the myocardium commences about 20 minutes after the onset of ischemia.<sup>5</sup> Reperfusion studies indicate that about 35% of the tissue destined to undergo necrosis is already beyond recovery 40 minutes after coronary occlusion and that when 6 hours have elapsed the percentage has increased to 90%.<sup>6</sup> If the results of these animal experiments

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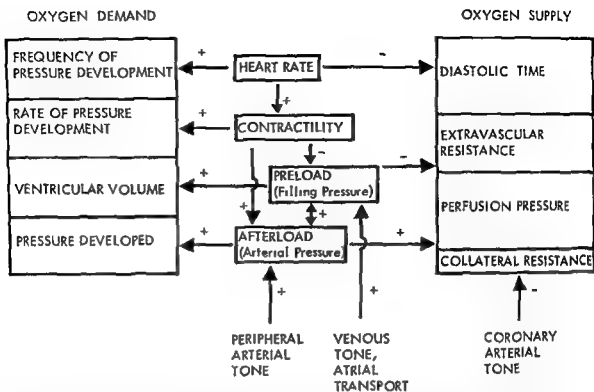


Fig 1 Factors influencing myocardial oxygen economy. Interactions positive or negative between the factors are indicated by arrows. Because of these interactions the net effect of an intervention cannot always be predicted (From Pantridge J P. *The Acute Coronary Attack*. Grune & Stratton Inc. 1975. New York and Pitman Medical Tunbridge Wells England. Reproduced by permission.)

are applicable to clinical myocardial infarction interventions initiated later than one hour after the onset of the coronary attack are likely to be of limited value in the prevention of infarct extension and the longer the delay the less will be the effect of therapy.

The quantity and precise geometry of myocardium which is critically ischemic at any one time following coronary occlusion is unknown. Nevertheless, the demonstration that death of perhaps half of the ischemic tissue takes place during the 5 hour period after the end of the initial 40 minutes of ischemia indicates clearly that a potential for modifying importantly the magnitude of the infarct exists. Where a mobile coronary care unit is available one half of the patients can be treated within 1 hour 40 minutes after the onset of symptoms. In places where prehospital coronary care is available limitation of the mass of myocardium destroyed is a practical proposition.

#### Oxygen economy of ischemic myocardium

While the object of early intervention is to obtain the most favorable balance between work

and useful pressure the simultaneous reduction of myocardial work and increase in perfusion pressure derived from cardiac contraction is rarely achieved. The factors affecting myocardial oxygen economy are summarized in Fig 1. Ischemic myocardium performs relatively little work but experimental evidence indicates that increasing myocardial work is harmful directly or indirectly to jeopardized myocardium.<sup>8</sup> Myocardial oxygen requirement depends on heart rate, the inotropic state and tension development (which in turn is dependent on developed pressure and the volume of the left ventricle in early systole according to the Laplace law).<sup>9</sup> "Coronary blood flow is affected by arterial pressure, left ventricular diastolic pressure (which when elevated limits flow to the endocardium), diastolic time and coronary vascular tone."<sup>10</sup> Coronary flow is severely restricted when the mean arterial pressure falls below 70 mm Hg.<sup>11</sup> Peripheral as well as central hemodynamics may be disturbed following myocardial infarction.<sup>12</sup>

It is clear that tachycardia, hypotension, left ventricular defeat and inappropriate increase in myocardial contractility which may result from

catecholamine secretion will be harmful in the presence of ischemia. The effects of bradycardia will also be deleterious if a slow heart rate results in hypotension. Hypertension might be expected to be beneficial since the resultant increase in coronary flow might exceed the increase in myocardial oxygen requirement.<sup>22</sup> Induced hypertension has indeed been shown to have salutary effects in the presence of experimental coronary artery stenosis.<sup>23</sup> Nevertheless there is evidence that the correction of hypertension has salutary effects on ischemic myocardium in patients with myocardial infarction.<sup>24</sup> It is likely that in the usual clinical situation an increase in left ventricular diastolic pressure which may be associated with hypertension combines with the increase in developed pressure to negate the benefit resulting from the improvement in coronary perfusion pressure. In addition, hypoxic myocardium contracts poorly against a high resistance.

The role of coronary vascular resistance and in particular collateral resistance in determining the magnitude of the infarct is difficult to evaluate. Spasm at sites of organic arterial disease has been reported to occur commonly in clinical infarction. Agents affecting vascular resistance in the region of the ischemic zone inevitably also affect the peripheral vessels and left ventricular filling pressure. Nitroglycerin has been shown to have a dilating effect upon coronary collateral vessels in man.

At a time when myocardial reserve has been impaired by the development of ischemia any additional myocardial work or reduction in arterial pressure to hypotensive levels resulting from inappropriate constriction or dilatation of peripheral vessels is likely to be harmful. Not only may the systemic vascular resistance be abnormal but changes in venous tone may reduce or increase venous return to the heart. An inappropriately low filling pressure or an acute reduction in preload appears to predispose to the development of the bradycardia-hypotension syndrome.<sup>25</sup> Venoconstriction will result in left ventricular failure disproportionate to the degree of reduction in ventricular performance. This situation is not infrequently seen during the course of hemodynamic investigations. Venoconstriction may persist for as long as 3 days after infarction.

The mechanical properties of the ischemic myocardium alter during the hours following coronary occlusion. The infarcting tissues swell

and become stiff.<sup>26, 27</sup> The swelling causes compression of the vessels supplying jeopardized myocardium and may cause extension of the infarct in the absence of other adverse hemodynamic changes. Stiffening is associated with stretching the ischemic region assumes larger dimensions but becomes less distensible.<sup>28</sup> The paradoxical pulsation evident immediately after experimental coronary occlusion is then reduced.<sup>29</sup> The remaining myocardium therefore works more effectively as a pump but any overall increase in ventricular volume resulting from stretching of the ischemic zone will increase oxygen requirements.

Ischemic myocardium which is still mechanically active produces a sustained contraction since relaxation is delayed.<sup>30</sup> This loss of synchronous activity reduces the mechanical efficiency of the ventricle and compresses the intramural vessels early in diastole when coronary perfusion pressure is maximal.

#### Clinical approach to the salvage of ischemic myocardium

The simple measures that have been employed to limit infarct size involve immediate correction of dysrhythmias, correction of the autonomic disturbance and management of clinically apparent hemodynamic abnormalities.<sup>31</sup> Relief of pain and anxiety will contribute to the correction of autonomic disturbance and by reducing restlessness will decrease cardiac work. The peripheral redistribution of blood resulting from the administration of diamorphine or its analogues will also have salutary effects if the left ventricular filling pressure is elevated.

Autonomic disturbance is common at the onset of infarction. Among patients seen within 30 minutes only 17% will have a normal heart rate and normal blood pressure. Sympathetic overactivity with tachycardia or transient hypertension or both will be evident among one third. Parasympathetic overactivity with bradycardia hypotension or both will be evident in approximately 50%.<sup>32</sup>

Bradycardia should have a salutary effect since it will be associated with a reduction in oxygen demand. Unfortunately among patients with bradycardia seen immediately after the onset of infarction 78% will show associated hypotension with a systolic blood pressure not greater than 100 mm Hg. In many of these patients the mean

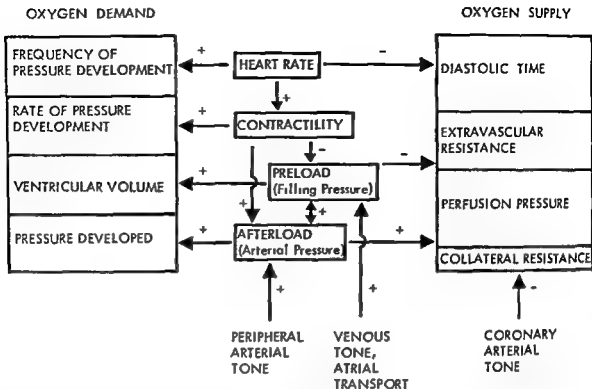


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It is clear that tachycardia, hypotension, left ventricular defeat and inappropriate increase in myocardial contractility which may result from

increasing collateral blood flow or the rate of diffusion of substrates and metabolites through ischemic tissue, the stabilization of ischemic cells, the provision of metabolic support, and improvement in arterial oxygenation. No attempt will be made to enumerate completely the multitude of techniques so far devised.

The difficulties in establishing the efficacy of a given therapeutic regime lie in the caution required in the application of the results of animal experiments to the clinical situation and in the problems of measuring the effects of the intervention on clinical myocardial infarction. In addition, the wide variation in experimental results must be interpreted in the light of the time after coronary occlusion at which therapy was initiated. It is also important to define clearly the clinical situations in which each therapeutic regime is likely to be salutary. For example, experimental elevation of the arterial pressure may be salutary in the absence of left ventricular failure but detrimental when ventricular function is poor and the effects of digitalis on ischemic myocardium are the reverse of those of raising the arterial pressure in both these situations.<sup>14</sup>

**Monitoring the effects of interventions.** The possibility of detecting changes in the intensity of ischemia in clinical myocardial infarction has received much attention in recent years. Only non-invasive methods are suitable for the assessment of the effects of therapy on large numbers of patients. Since myocardial function is closely related to intensity of ischemia, it is possible that two-dimensional echocardiography and radionuclide imaging techniques for monitoring regional myocardial contraction will in the future contribute to the assessment of the results of interventions. Difficulties in the use of such methods are likely, since the effects of treatment will have to be interpreted against the background of rapidly evolving mechanical properties of the ischemic zone. Factors such as arterial pressure may affect contraction independently of local ischemia.

At present, the emphasis is on enzymatic and electrocardiographic techniques.

**Creatine kinase release.** The quantity of the enzyme creatine kinase which appears in the peripheral blood following release from moribund cells is regarded as a parameter of the magnitude of the infarct.<sup>15</sup> A modification of the method of Shell, Sobel, and co-workers, devised by Norms

and co-workers<sup>16</sup> has been used in a number of investigations. The modification involves calculation of the disappearance rate of the enzyme for each patient. This calculation may be subject to inaccuracies<sup>17</sup> and the use of an average disappearance rate is still preferred by some workers. Plasma levels of the enzyme are corrected, cumulatively for estimated loss. The accuracy of the method is impaired if the patient is given intramuscular injections which result in enzyme release from skeletal muscle. This difficulty may be circumvented if the MB fraction of the enzyme is measured, since this fraction is specific for the myocardium.<sup>1</sup>

Attempts have been made to predict the remainder of the release curve from the points obtained during the few hours after the onset of enzyme release.<sup>18</sup> This curve may then be compared with that obtained following therapy. A reduction in enzyme release in comparison with that expected would suggest that the effects of therapy have been salutary.<sup>19, 20</sup> A major disadvantage of this approach is that therapy must be withheld for some hours while the early blood samples are obtained. Unfortunately, after such delay, the possibility of limiting infarct size is minimal.

The enzymatic method has another important limitation. The removal of creatine kinase from the circulation is largely independent of the hemodynamic situation.<sup>1</sup> However, the fraction of the enzyme which appears in the peripheral blood, usually about 30%, is inversely related to the interval between the release into the interstitial fluid and passage through lymphatics into the blood stream. An improvement in blood supply to the ischemic region may increase the rate of flow of interstitial fluid into the lymphatics and hence the proportion of the enzyme released which appears in the peripheral blood. An erroneous impression that ischemia had been intensified might result.<sup>1</sup>

**ST segment elevation.** Measurements of the magnitude of ST segment elevation recorded from multiple leads on the precordium give some indication of the instantaneous intensity of ischemia, affecting the underlying myocardium.<sup>21</sup> A reduction in ischemia will usually result in a lowering of the ST segments and an increase will have the reverse effect. Unfortunately, interventions which influence ischemia such as variations in heart rate or sympathetic activity



ty may also have direct effects on the action potentials in both ischemic and non ischemic regions. Changes in action potential morphology may alter the level of the ST segment.<sup>33</sup> Such alterations will occur independently of any effect on ischemia. In addition an agent such as insulin might reduce elevated extracellular potassium levels in the ischemic zone increase diastolic polarization of the cells and reduce the injury current. The effects of such an agent on the ST segment need not necessarily imply improvement in ischemia or improved cellular prognosis.

Caution is certainly required in interpreting ST segment displacement. Although, in the experimental animal, the sum of ST elevations at multiple precordial sites is closely related to the corresponding epicardial measurements.<sup>34</sup> Smith and co workers were unable to demonstrate a simple quantitative relationship between ST segment elevation recorded from the epicardial surface of the canine heart and blood flow in the subjacent myocardium. An increase in the size of the ischemic zone may actually reduce the magnitude of the injury current at epicardial sites.<sup>35</sup> Nevertheless Angell and colleagues found a significant correlation between ST segment elevation at individual sites and intramyocardial O<sub>2</sub> tension 4 mm below the epicardial surface. Measurements of ST segment displacement are invalid in records where intraventricular conduction block is apparent. The limitations of ST segment mapping have been considered in detail by Fozzard and DasGupta. Despite these limitations the technique may have a place in the assessment of ischemia.<sup>36</sup> The effects of the complex geometric relationship between boundaries separating ischemic and non ischemic tissues and the electrocardiogram have been analyzed by Holland and Brooks.

**Projection of QRS changes from early injury current.** Recently a series of electrocardiographic techniques has been developed which appears to be free from many of the problems associated with limiting the measurements to the ST segment. The changes in the QRS complex resulting from infarction have been shown to be related to infarct size in the open-chest dog and to be predictable from the early displacement of the ST segment.<sup>37</sup> The predictive value of ST segment elevation in the standard leads in relation to R wave diminution and the appearance of Q waves has been confirmed in the clinical situation. The

predictive value of ST elevation in relation to QRS change in precordial maps from patients with anterior infarction has also been confirmed.<sup>38</sup> The time after onset of symptoms at which the leads showing ST elevation are assessed is of critical importance in estimating the likelihood of disappearance of R waves.<sup>39</sup>

An intervention introduced following the initial record may be shown to have altered the degree of change in the QRS complex to an extent which lies outside the limits of that expected. The method is independent of any direct effect of therapy upon the ST segments and seems the most promising of the techniques currently available.

**Reduction of elevated filling pressure.** Elevation of the left ventricular filling pressure is rare when the heart rate is slow but clinically important left ventricular defeat mild or moderate in degree is common among patients with normal or rapid rates. Patients with anterior infarction have on average higher filling pressures than those with posterior infarction.<sup>40</sup> When the filling pressure is elevated a reduction may be effected by administration of a vasodilator agent. There is evidence that substances such as sodium nitroprusside which dilate resistance vessels are unsatisfactory for this purpose since they reduce myocardial perfusion whereas nitroglycerin increases blood flow in the ischemic zone.<sup>41</sup> The superiority of nitroglycerin may be explained by local effects on the coronary circulation but it may be relevant that in patients nitroglycerin a selective venodilator, caused a greater reduction in left ventricular filling pressure and a smaller reduction in arterial pressure than did sodium nitroprusside. The data of Armstrong and associates confirm that nitroglycerin selectively reduces the preload and that sodium nitroprusside has relatively greater effects on afterload and coronary perfusion pressure.

Clinical evidence suggests that administration of nitroglycerin may reduce the extent of ischemia.<sup>42</sup> However results from the animal laboratory indicate that if reduction in filling pressure is excessive hypotension with reflex tachycardia may result with possible intensification of ischemia. Nitroglycerin may also precipitate bradycardia and hypotension in patients.<sup>43</sup> The addition of a vasoconstrictor agent such as methoxamine or phenylephrine in doses sufficient to prevent tachycardia and hypotension will

result in greater improvement in the ischemic zone than will the administration of nitroglycerin alone.<sup>14</sup> Indiscriminate use of vasoconstrictor agents in conjunction with nitroglycerin cannot however be recommended since phenylephrine may partially reverse the salutary effect of nitroglycerin in patients with left ventricular failure.<sup>1</sup>

Nitroglycerin has been administered by the sublingual route to patients with myocardial infarction without ill effect.<sup>15</sup> However slow intravenous infusion is the only technique by which effective doses can be given safely over a period. Titration of the individual dose is necessary with careful monitoring of the heart rate and blood pressure.<sup>16</sup> Administration of nitroglycerin is complicated by absorption of the drug by the tubing of the infusion equipment.<sup>1</sup> Nevertheless nitroglycerin is the most effective venodilator agent available and if a relatively simple regime for its intravenous administration can be developed it may find a place in the management of a substantial proportion of patients with acute infarction.

It has recently been shown that in the absence of infarction nitroglycerin administration increases left ventricular compliance. A possible mechanism for this effect is a reduction in pressure applied to the interventricular septum from the right ventricular cavity. An adequate cardiac output may therefore be maintained by improved diastolic function of non-ischemic myocardium despite reduction in filling pressure.<sup>17</sup>

**Increasing osmotic pressure of extracellular fluid.** Osmotically active agents such as hypertonic mannitol increase collateral blood flow in the presence of ischemia probably by reducing the swelling of ischemic cells.<sup>18</sup> The reduction in coronary vascular resistance associated with mannitol administration following prolonged coronary occlusion apparently includes reduction in the resistance of the vessels in the vulnerable subendocardial zone of the left ventricle.<sup>19</sup> However mannitol exerts a direct positive inotropic effect<sup>20</sup> which may be undesirable. Powell and co-workers<sup>21</sup> observed that mannitol had a salutary effect when coronary occlusion lasted 1 hour or less but Hurzel and Kirk<sup>22</sup> were unable to demonstrate any reduction in myocardial damage when mannitol was administered during prolonged coronary occlusion. Since reper-

fusion of formerly ischemic areas resulting from correction of autonomic disturbances may cause swelling of the tissues there may be a place for mannitol administration in conjunction with other interventions which are likely to improve blood flow to the ischemic zone.

**Pharmacological use of beta adrenergic blocking drugs.** While the value of beta blocking agents in the control of sympathetic overactivity is undoubted the possibility that these drugs may help to preserve jeopardized myocardium irrespective of the level of sympathetic activity has been investigated. There is ample experimental and some clinical evidence that beta blocking agents may prevent hypoxic damage or limit the effects of ischemia.<sup>23-25</sup> In addition to the salutary effects on the myocardium ischemic microvascular injury may be reduced.<sup>26</sup> It has been suggested that propranolol may prevent myocardial necrosis in some patients who would otherwise have developed infarction. The administration of these agents to patients with bradycardia or hypotension is however contraindicated. Furthermore bradycardia may follow their administration. The routine use of beta adrenergic blocking drugs as a means of limiting infarct size cannot be recommended unless the patient is to be continuously monitored so that bradycardia may be immediately detected.

**Verapamil and nifedipine.** Verapamil like the beta blocking drugs reduces cardiac work and in addition causes vasodilatation and may also have salutary effects.<sup>27</sup> A further beneficial effect of verapamil and of the newer agent nifedipine is the release of coronary artery spasm which may be important in some patients.

**Agents acting at tissue level.** In the experimental situation the enzyme hyaluronidase has been shown to be effective in salvaging ischemic myocardium.<sup>28-30</sup> Preliminary clinical evidence supports the experimental results. Hyaluronidase may act by improving diffusion of substrates through ischemic tissue. Another possible mechanism is the preservation of collateral blood flow.

Corticosteroid hormones in high dosage have been found to limit the effects of ischemia in the experimental animal.<sup>31</sup> Steroids may act by preserving intracellular architecture and by improving metabolism and collateral blood flow.<sup>32</sup> but evidence of benefit in clinical myocardial infarction is conflicting.<sup>33-35</sup> A recent exper-

mental investigation of the effects of methylprednisolone on final infarct size did not demonstrate any benefit, and the results suggested that the steroid increased ventricular irritability.<sup>10</sup> The data of Yoon and associates<sup>11</sup> do not however support the latter proposition.

It has been suggested that the presence of any salutary effect of corticosteroids is limited to the first few hours after the onset of infarction.<sup>12</sup> The high affinity of cardiac tissue for steroids falls rapidly following the development of ischaemia.

Potassium is rapidly depleted from ischemic cells, and aerobic metabolism of glucose is depressed. A regime consisting of glucose, insulin, and potassium (GIK) was devised by Sodi-Pallares and co-workers<sup>13</sup> with the object of reducing the amount of potassium lost. Opie<sup>14</sup> suggested that the regime may be beneficial through stimulation of glucose metabolism and reduction in the level of circulating free fatty acids (FFA).

Oliver<sup>15</sup> suggested that the possible salutary effects of therapeutic reduction of elevated FFA levels and of the stimulation of glucose uptake by the myocardium required further investigation. However the relevance of the detrimental effects of experimental elevation of FFA on ischemic cardiac tissue has been questioned.<sup>16</sup> Nevertheless, evidence that increased catecholamine concentrations potentiate the adverse effects of FFA on the myocardium supports the hypothesis that FFA may have clinical relevance.<sup>17</sup>

The administration of GIK following coronary occlusion in the dog resulted in a reduction in plasma FFA levels, and a decrease in FFA uptake and an increase in glucose uptake by the myocardium. These effects were associated with evidence of metabolic improvement at the periphery of the ischemic zone.

The potential salutary effects of the constituents of the GIK regime are not restricted to the reduction of elevated FFA levels. Following coronary occlusion in a rat heart preparation glucose and insulin each reduced the release of cardiac enzymes resulting from the presence of fairly constant concentrations of FFA.

It is quite possible that elevated FFA levels in patients with myocardial infarction are indeed detrimental to jeopardized myocardium, and that reduction in these levels and of myocardial FFA uptake represent one important mechanism of

the action of GIK therapy. Patients with relatively large infarcts have on average higher plasma FFA concentrations than those whose infarcts are small.<sup>18</sup> It has been proposed that high FFA levels play a part in promoting the vicious circle of extending infarction.<sup>19</sup>

As in the dog GIK had favorable metabolic effects on infarcting baboon myocardium. Other experimental evidence indicates that the GIK regimen will have salutary effects on jeopardized myocardium.<sup>20</sup> Clinical evidence of such benefit is still, however lacking.<sup>21</sup>

**Administration of oxygen.** Hypoxemia is detrimental to ischemic myocardium.<sup>22</sup> Moreover there is evidence that a moderate increase in inspired oxygen concentration above 20% may be salutary.<sup>23</sup> The data of Madias and co-workers<sup>24</sup> suggest that myocardial hypoxia may be reduced when oxygen in high concentration is administered to patients with myocardial infarction. These results support the already widespread clinical practice of administering oxygen even in the absence of signs of hypoxia.

## Conclusion

It is clear that further work is required to define the place of the more recently introduced regimes in the routine management of patients with myocardial infarction. It is, however, important to recognize that shock may usually be prevented by such simple measures as the timely relief of pain and the immediate correction of disturbances of heart rate and rhythm and of blood pressure. Such disturbances commonly result from autonomic imbalance.

The crucial point in prevention of shock is the early initiation of therapy. Resources directed toward this end will undoubtedly result in greater reward than their direction toward complex circulatory support systems.

Fig. 1 is reproduced by kind permission of Pitman Medical, Tunbridge Wells, England.

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# Appraisal and reappraisal of cardiac therapy

Edited by Arthur □ DeGraff and Julian Frieden

## Clinical pharmacology of the new beta-adrenergic blocking drugs Part 10 Beta adrenoceptor blockade and coronary artery surgery

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Beta adrenoceptor blocking drugs are important therapeutic agents in the medical management of patients with angina pectoris hypertension cardiac arrhythmias thyrotoxicosis pheochromocytoma and obstructive cardiomyopathies. An increasing number of patients can be expected to present for surgical anesthesia while taking beta adrenoceptor blocking drugs.

During the past several years recommendations regarding treatment of patients receiving propranolol and who were scheduled for coronary artery bypass operations have varied widely. These recommendations have ranged from the complete withdrawal of therapy two weeks prior to surgery to the continuation of therapy at the same or lesser dosage just prior to the operation. Reports associating the abrupt withdrawal of long term propranolol therapy with an increase in angina new arrhythmias myocardial infarction or sudden death have raised the issue of whether the risk of such withdrawal before coronary bypass operation is greater than the risk

of purported myocardial depression attributed to interaction between residual  $\beta$  adrenoceptor blockade and general anesthesia.

Recent retrospective and prospective reviews of consecutive coronary artery bypass operations in which propranolol therapy was not withdrawn for medical indications failed to identify any deleterious interaction between anesthesia and preoperative propranolol administration.<sup>1-3</sup> Moreover anesthetic agents commonly used for bypass operations have been shown in animals not to potentiate the effects of propranolol.

In a previous study in patients who underwent coronary artery bypass surgery, our group described a higher incidence of postoperative arrhythmias and hypertension in individuals withdrawn from propranolol preoperatively when compared to a population who either never received the drug or had the drug maintained postoperatively.<sup>4</sup> We therefore undertook this prospective study to elucidate the mechanism for these phenomena. Our protocol was designed to answer the following questions: (1) Are there hazards associated with either preoperative maintenance or withdrawal of propranolol therapy? (2) Are there hazards related to persisting  $\beta$  blockade during intubation general anesthesia and coronary artery bypass surgery? (3) Does persisting  $\beta$  blockade lead to poor cardiac per-

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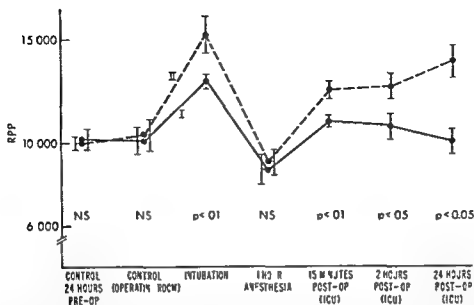


Fig 1 Mean rate-pressure product (RPP) of group I patients (no propranolol) and group II patients (propranolol discontinued 48 hours preop) before, during and after coronary artery surgery. Group I is shown with a solid line group II with a broken line. Group II patients demonstrate a significant increment in RPP during intubation and the postoperative intervals when compared to group I patient. The values refer to the differences between groups at the different study intervals. NS = not significant.

Table II Characteristics of patient groups

Group	Patient number	Age (years)	Sex	LV EDP mm Hg	% of Grafts	Propranolol dose (mg/day)	Previous myocardial infarct (# of group)	Previous hypertension (# of group)
			M/F					
I	17	59 ± 1	11/6	14 ± 1	33 ± 0.2	—	23 <sup>a</sup> (4/17)	30 <sup>a</sup> (6/17)
II	17	53 ± 2	11/6	14 ± 1	73 ± 0.2	154 ± 18	23 <sup>a</sup> (4/17)	41 <sup>a</sup> (7/17)
III	18	57 ± 2	12/6	15 ± 2	24 ± 0.2	151 ± 15	29 <sup>a</sup> (3/18)	28 <sup>a</sup> (3/18)
IV	18	56 ± 2	11/8	15 ± 1	75 ± 0.2	133 ± 0	26 <sup>a</sup> (5/19)	32 <sup>a</sup> (6/19)

Abbreviations: LV EDP = left ventricular end-diastolic pressure.

plications as well as the need for cardioactive agents until hospital discharge were recorded.

Blood specimens for plasma propranolol levels were obtained at the time of induction after cardiopulmonary bypass and immediately upon arrival in the intensive care unit. Measurements were made using the modified fluorometric method of Coltart and Shand.

Blood specimens for plasma renin activity were obtained several times in the operating room prior to induction (control), immediately after intubation and following surgery (15 minutes and 2 hours). The renin measurements were made

by the radioimmunoassay technique of Chervu and associates.<sup>22</sup>

The significance of differences in incidence between groups was determined by chi-square analysis and differences in means of quantitative data were derived using Student's *t* test for non-paired data. The standard error of the mean was used as the index of dispersion.

## Results

The four patient groups were remarkably homogenous for patient characteristics such as sex, history of hypertension and previous myocardial

**Table III** Effects of different propranolol regimens on heart rate systolic blood pressure and rate pressure product in patients undergoing coronary artery bypass surgery

Observation period	Group I (no pro pranolol)	Group II (propranolol stopped 48 hrs preop)	Group III (propranolol stopped 10 hrs postop)	Group IV (propranolol stopped 2 hrs preop contin ued postop)	Group 1 ts	Group 1 ts
					Group 2	Group 3
Control (24 hrs preop)						
hr	79 ± 3	76 ± 3	72 ± 2	70 ± 2	NS	NS
bp	131 ± 4	132 ± 3	122 ± 6	125 ± 3	NS	NS
rpp	10 200 ± 485	10 000 ± 364	8 500 ± 436	8 600 ± 252	NS	<0.01
Control (immed preop)						
hr	78 ± 4	79 ± 3	66 ± 5	67 ± 3	NS	<0.01
bp	130 ± 6	132 ± 4	118 ± 5	114 ± 3	NS	NS
rpp	10 100 ± 655	10 400 ± 752	7 700 ± 485	7 700 ± 275	NS	<0.05
Intubation						
hr	71 ± 2	80 ± 2	84 ± 4	71 ± 3	<0.01	<0.01
bp	180 ± 7	190 ± 6	173 ± 7	154 ± 5	NS	Nb
rpp	13 000 ± 364	15 300 ± 846	14 500 ± 1 116	11 200 ± 458	<0.01	NS
1 hr anesthesia						
hr	73 ± 4	76 ± 4	75 ± 3	88 ± 1	NS	NS
bp	115 ± 5	120 ± 4	125 ± 7	108 ± 4	NS	NS
rpp	8 742 ± 723	9 100 ± 631	9 235 ± 543	7 817 ± 596	NS	Nb
15 min postop (ICU)						
hr	84 ± 3	97 ± 3	88 ± 2	80 ± 3	<0.01	NS
bp	132 ± 3	131 ± 4	132 ± 5	135 ± 4	NS	NS
rpp	11 100 ± 249	12 600 ± 436	11 700 ± 631	10 400 ± 435	<0.01	Nb
2 hrs postop (ICU)						
hr	84 ± 7	96 ± 4	111 ± 5	79 ± 2	NS	Nb
bp	130 ± 4	136 ± 3	144 ± 7	136 ± 3	Nb	NS
rpp	10 800 ± 655	12 800 ± 582	13 300 ± 800	10 400 ± 435	p<0.05	p<0.05
24 hrs postop (ICU)						
hr	84 ± 2	105 ± 5	96 ± 3	77 ± 2	<0.01	<0.01
bp	116 ± 3	137 ± 7	140 ± 7	120 ± 4	<0.01	<0.01
rpp	10 100 ± 582	14 000 ± 776	13 400 ± 946	9 300 ± 389	<0.05	<0.05

dial infarction duration of anesthesia duration of cardiopulmonary bypass and number of coronary vessels bypassed. There were no differences between the groups in the ease of discontinuing cardiopulmonary bypass.

There were five perioperative infarctions (new Q waves) seen with one death. The incidence of infarction among the different groups was: group I 6% (1 of 17), group II 18% (3 of 17), group III 6% (1 of 18), group IV 0% (none of 19). The one death occurred in a group II patient 28 hours after surgery from low cardiac output as a consequence of infarction.

The hemodynamic results are shown in Table III and in Figs 1 to 6. During the control period (24 hours prior to surgery) patients in groups III and IV (both groups still receiving propranolol) had significantly lower mean rate pressure products (RPP) than group I and II patients. During

the control period immediately prior to surgery patients in groups III and IV continued to have significantly lower RPP than group I and II patients.

With intubation there was a dramatic increase in RPP in all four groups predominantly due to a marked systolic blood pressure elevation (in some patients up to 280 mm Hg). However the RPP increment in group IV patients was significantly blunted compared to groups I to III. At the same time the RPP value for group IV was significantly lower than that of the other three groups. Group I patients (no propranolol) also had a lower RPP increment than group II and III patients.

After one hour of halothane anesthesia the blood pressure and RPP returned to near control levels (24 hours preop) for all groups, however group IV continued to have a significantly lower RPP than the other three groups.

## Statistical Significance

Group 1 vs Group 4	Group 2 vs Group 3	Group 2 vs Group 4	Group 3 vs Group 4
<0.01	NS	NS	NS
NS	NS	NS	NS
<0.01	<0.05	<0.01	NS
<0.01	<0.05	<0.01	NS
<0.01	<0.05	<0.01	NS
<0.05	<0.01	<0.01	NS
NS	NS	<0.05	<0.05
<0.05	NS	<0.01	<0.01
<0.01	NS	<0.01	<0.01
<0.05	NS	<0.05	<0.05
NS	NS	<0.05	<0.05
NS	NS	NS	<0.05
NS	<0.05	<0.01	<0.05
NS	NS	NS	NS
NS	NS	<0.01	NS
NS	NS	<0.01	<0.05
NS	NS	NS	NS
NS	NS	<0.01	<0.01
<0.05	NS	<0.01	<0.01
NS	NS	<0.05	<0.05
NS	NS	<0.01	<0.01

Fifteen minutes following surgery in the ICU the RPP was found to rise in all four groups (though not as markedly as during intubation). Group II patients had the highest increment in both pulse rate and RPP compared with the three other groups. Group I and group IV patients appeared to react similarly.

Two hours later patients in group III were found to have a greater increment in heart rate and RPP compared to 15 minutes postop. At this point groups II and III were similar with a higher heart rate and RPP than groups I and IV.

Twenty four hours post surgery the heart rate, blood pressure and RPP continued to climb in both groups II and III (with the RPP almost to the level found during intubation). The blood pressure, heart rate and RPP in groups I and IV remained significantly lower than in groups II and III.

There was a significant difference in the incidence of supraventricular arrhythmias among the four study groups (Table IV Fig 7) during the initial 24 hour postoperative period. In group I seven patients remained in normal sinus rhythm and 10 developed supraventricular arrhythmias (six sinus tachycardia >110, four paroxysmal supraventricular tachycardia or atrial flutter). Group II patients had the highest incidence of supraventricular arrhythmias among the four study groups. One patient remained in normal sinus rhythm and 16 developed supraventricular arrhythmias (eight sinus tachycardia >110 and eight paroxysmal supraventricular tachycardia or atrial flutter/fibrillation). Group III patients also had a high incidence of supraventricular arrhythmias. Three patients remained in normal sinus rhythm and 15 developed arrhythmias (seven sinus tachycardia >110, eight paroxysmal supraventricular tachycardia or atrial flutter/fibrillation). The incidence of arrhythmia was significantly higher in group II ( $p < 0.01$ ) and group III ( $p < 0.05$ ) when compared to groups I and IV. Group IV had a significantly lower incidence of supraventricular arrhythmia than the other three treatment groups ( $p < 0.01$ ). Fourteen patients were in normal sinus rhythm and five developed arrhythmias (three sinus tachycardia >110 and two paroxysmal atrial tachycardia or atrial flutter/fibrillation). All paroxysmal arrhythmia episodes in each group responded to intravenous propranolol (or supplementary propranolol in group IV patients). Ventricular arrhythmias were rarely seen in the initial 24 hour postoperative period.

Plasma renin activity (PRA) was lower in group IV patients compared to all other groups throughout the control intubation and postoperative periods. There were no significant differences in PRA between groups II to IV during the intubation and postoperative intervals. Comparing group I and IV the results were: control (operating room) group I  $1.13 \pm 0.04$  ng/ml/hr, group IV  $0.96 \pm 0.11$  ng/ml/hr, after intubation group I  $1.36 \pm 0.26$  ng/ml/hr, group IV  $0.98 \pm 0.12$  ng/ml/hr, 15 minutes postoperation group I  $1.86 \pm 0.10$  ng/ml/hr, group IV  $0.95 \pm 0.15$  ng/ml/hr ( $p < 0.01$ ). 2 hours postoperation group I  $1.66 \pm 0.53$  ng/ml/hr, group IV  $1.08 \pm 0.19$  ng/ml/hr.

Propranolol plasma levels at the time of intubation were negligible for group II patients and

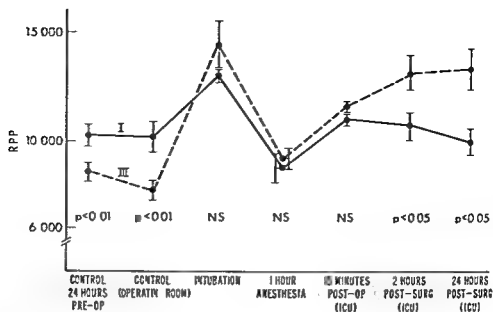


Fig 2 Mean rate pressure product (RPP) of group I patients (no propranolol) and group III patients (propranolol discontinued 10 hours preop) before during and after coronary artery surgery. Group I is shown with a solid line group III with a broken line. Group III patients had significantly lower RPP (probably due to persistence of beta adrenoceptor blocker effect) than group I during the preoperative intervals. However with intubation there is no difference between groups. Two hours and 24 hours postoperatively the RPP is significantly higher in group III patients compared to group I patients.

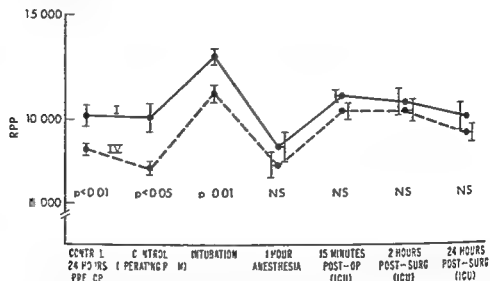


Fig 3 Mean rate pressure product (RPP) of group I patients (no propranolol) and group IV patients (propranolol maintained until 10 hours preop restarted immediately postop) before during and after coronary artery surgery. Group I is shown with a solid line group IV with a broken line. Group IV patients had significantly lower RPP than group I patient during the preoperative intervals. The increment in RPP with intubation was significantly blunted in group IV patients. The operative and postoperative differences in RPP between groups were not significant.

$9.32 \pm 0.82$  ng/ml in group III patients (minimal therapeutic level  $>40$  ng/ml). One hour after cardiopulmonary bypass the drug level in group III declined progressively to  $3.7 \pm 0.20$  ng/ml so that in the immediate postoperative period it was negligible  $2.26 \pm 0.22$  ng/ml. Renal clear-

ance of propranolol increased considerably during cardiopulmonary bypass. Group IV patients had a plasma propranolol level of  $39.1 \pm 1.17$  ng/ml at the time of induction which decreased considerably post cardiopulmonary bypass to  $5.2 \pm 0.60$  ng/ml.

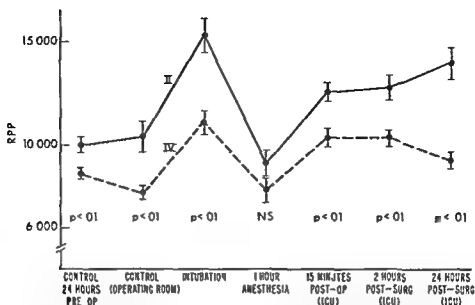


Fig 4 Mean rate pressure product (RPP) of group II patients (propranolol discontinued 48 hours preop) and group IV patients (propranolol maintained until 2 hours preop restarted immediately) before during and after coronary artery surgery. Group II is shown with a solid line group IV with a broken line. Group IV patients had significantly lower RPP at each study interval compared to group II patients.

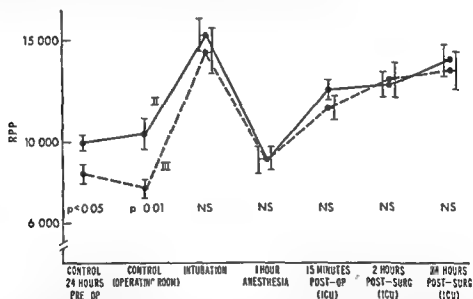


Fig 5 Mean rate pressure product (RPP) of group II patients (propranolol discontinued 48 hours preop) and group III patients (propranolol discontinued 10 hours preop) before during and after coronary artery surgery. Group II is shown with a solid line group III with a broken line. Group III patients had significantly lower RPP during the preoperative periods; however, there were no differences between the groups during the other study intervals. A marked increment in RPP during intubation and the postoperative periods was seen.

## Discussion

Since the discovery by Powell and Slater<sup>23</sup> that the dichloro analogue of isoproterenol could completely inhibit the effects of catecholamines on the heart, a number of beta adrenoceptor blocking agents have been synthesized and subjected to

clinical evaluation. Although the therapeutic value of these drugs is well established for angina pectoris, hypertension, arrhythmias, hypertrophic obstructive cardiomyopathy, thyrotoxic tachycardia, and pheochromocytoma, the attitudes of anesthesiologists and surgeons to their



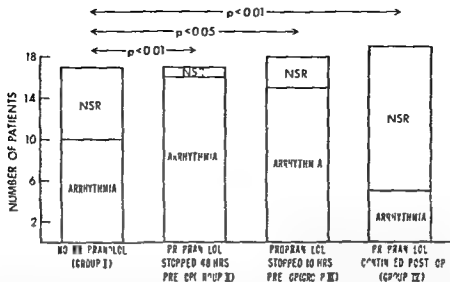


Fig 7 The incidence of supraventricular arrhythmias post-coronary artery bypass in the different propranolol treatment groups. There was a significant increase in the frequency of arrhythmias in group II patients (propranolol discontinued 48 hours preop) and group III patients (propranolol discontinued 10 hours preop) compared to group I (no propranolol). Group IV patients (propranolol maintained postop) had a significantly lower incidence of arrhythmias compared to group I patients (no propranolol).

nary artery disease who received propranolol (100 to 320 mg) to within 24 hours of surgery, four of these patients died and one had a stormy postoperative course. The authors concluded that propranolol was a major factor in these deaths and therefore recommended that it be discontinued for two weeks before operations. However, close scrutiny reveals that these five cases were complicated by other factors and it is difficult to implicate propranolol alone as the cause for the complications seen.

In 1973 Faulkner and colleagues demonstrated that any negative inotropic effects of propranolol had disappeared by 48 hours and suggested that the recommendation of Viljoen and colleagues for a two week preoperative withdrawal period was unfounded.

In 1974 Caralps and associates reviewed 100 cases of coronary artery bypass surgery including 20 patients who were receiving 40 to 200 mg of propranolol 24 hours or less before the operation. They revealed that the operative course of patients receiving propranolol many of whom had unstable angina was no different from that of untreated patients. In a larger review of 303 patients who underwent coronary artery surgery the same investigators found that propranolol treated subjects (48 hours or less prior to surgery) not only tolerated the operative procedure well

but demonstrated a low mortality rate (3.8% for patients receiving propranolol vs 6.6% for those never receiving the drug).

In 1975 Kaplan and associates reviewed the records of 169 consecutive patients undergoing coronary artery bypass surgery, of whom 143 had been taking propranolol with regard to preoperative administration of propranolol and intraoperative or postoperative complications. Patients taking propranolol until 24 hours before surgery showed no increased incidence of hypotension or bradycardia before cardiopulmonary bypass. Hypotension after bypass was no more common in patients off propranolol 12 to 48 hours than in patients who either discontinued the drug over 48 hours before operation or had never taken the drug. The operative mortality rate was 4% in patients taking propranolol within 48 hours of surgery and 6% in all other patients. The authors concluded that propranolol could be safely given within 12 to 48 hours of coronary artery surgery.

Kaplan and Dunbar<sup>1</sup> in 1976 also showed that patients with angina pectoris undergoing non cardiac surgical procedures and general anesthesia could safely tolerate propranolol administration to within 24 hours of operation.

The relative safety of maintaining propranolol just prior to surgery established by these retro



spective studies emphasized the need for a prospective study to delineate the true clinical interaction between propranolol and general anesthesia for coronary artery operations.<sup>9</sup> Reports associating the abrupt withdrawal of long term propranolol therapy with an increase in angina pectoris, new arrhythmias, myocardial infarction, or sudden death raised the issue as to whether the risk of such withdrawal before coronary bypass operation was greater than the risk of purported myocardial depression.<sup>10</sup>

The mechanism for the withdrawal reaction is unknown but since propranolol lowers myocardial oxygen requirements, abrupt withdrawal of the drug may then raise the oxygen requirements beyond what the coronary arteries can supply, resulting in severe ischemia or myocardial infarction.<sup>2</sup> Other postulated mechanisms include increased platelet aggregability,<sup>11</sup> hypersensitivity to circulating catecholamines (analogous to denervation hypersensitivity),<sup>12</sup> and reactivation of the renin-angiotensin-aldosterone mechanism.<sup>6</sup>

In a recent editorial, Shand and Wood<sup>13</sup> felt that the propranolol withdrawal syndrome was real but rare. Shroff and associates<sup>14</sup> found the syndrome to be rare in patients with angina pectoris who had their propranolol stopped abruptly prior to cardiac catheterization. The effect may have been blunted in Shroff's series because these patients had reduced in-hospital physical activity. However, a rebound effect following propranolol withdrawal may be more important in the setting of surgical stress. There is evidence that catecholamines and the level of adrenergic tone are elevated during laryngoscopy and intubation,<sup>15</sup> and again after saphenous vein coronary bypass.<sup>16,17</sup> There are marked increments in blood pressure demonstrated during intubation and a marked increase in heart rate, blood pressure, and arrhythmias in the immediate postoperative state.<sup>18</sup> Patients who have their propranolol stopped abruptly may become hypersensitive to catecholamines during these periods.

In a retrospective study by Langou and co-workers,<sup>19</sup> the risk of perioperative myocardial infarction was significantly increased by abrupt propranolol withdrawal 24 hours before coronary surgery compared to a gradual withdrawal regimen (32% infarct rate vs. 7% infarct rate).

Recent studies by Kirsh and associates,<sup>20</sup> Koppi-

va and colleagues,<sup>21</sup> and Boudoulas and co-workers<sup>22</sup> demonstrated the safety of propranolol administered within 1 to 5 hours of coronary artery surgery.

In a large prospective trial by Slogoff and associates,<sup>4</sup> chronic propranolol therapy was administered in full dosage just prior to surgery, and comparison was made with groups of patients where therapy was not given or where it was abruptly withdrawn 24 to 72 hours preoperatively. Patients abruptly withdrawn from their propranolol treatment had the highest incidence of intraoperative ischemia and arrhythmias, probably related to a higher rate-pressure product than was seen in patients where propranolol was maintained just prior to surgery. Hypotension and bradycardia were not more common in patients who had propranolol continued. Moreover, no differences among groups were noted in ease of discontinuation of cardiopulmonary bypass, need for cardiac stimulants, or in mortality rate.

In another recent prospective study, Boudoulas and colleagues<sup>23</sup> demonstrated that propranolol maintained prior to surgery in patients lowered the incidence of supraventricular tachyarrhythmias in the postoperative period when compared to patients where propranolol was abruptly discontinued 24 hours prior to surgery. There were no complications related to propranolol during the intraoperative period. The left ventricular function, as measured from systolic time intervals, was the same pre- and postoperatively with both treatment regimens.

Our group demonstrated a high incidence of supraventricular arrhythmias and hypertension following coronary artery bypass in patients with angina pectoris who had propranolol withdrawn greater than 48 hours prior to surgery when compared to patients who had the drug maintained just prior to surgery.<sup>18</sup> We postulated a propranolol withdrawal effect as the cause for these phenomena and carried out a trial described in this report using different preoperative propranolol treatment regimens with comparisons made with patients receiving no previous propranolol therapy.

The results of this study show that propranolol can be given safely to hemodynamically stable patients just before they undergo elective coronary artery bypass surgery. Propranolol-treated patients (group IV—drug maintained just prior to surgery and restarted postoperatively) had a sig-

nificant blunting of the hypertensive reflex usually seen during intubation<sup>31</sup> and demonstrated negligible changes in the rate pressure product in the postoperative period. A significant reduction in the incidence of supraventricular arrhythmias was also noted. Of concern was the finding that there were greater increments in systolic blood pressure and rate-pressure product during the intubation and postoperative periods in those patients where propranolol was stopped 10 to 48 hours prior to surgery (groups II-III) when compared to group I (no propranolol) and group IV patients. There was also a significantly higher incidence of arrhythmias seen in those patients who had propranolol abruptly withdrawn compared to group IV patients.

The data in this report suggest that there is a true propranolol withdrawal effect which becomes manifest during coronary artery surgery. This phenomenon does not appear to be mediated through the renin-angiotensin system as was previously suggested<sup>32-3</sup> but probably by a hyperadrenergic response to a stress situation.<sup>4</sup> The patients who never received propranolol did not demonstrate a large increment in rate-pressure product in the postoperative period despite having higher serum renin activity when compared to group IV patients (propranolol maintained). The marked increments in rate-pressure product (an indirect index of myocardial oxygen demand) and frequency of arrhythmia in the postoperative periods was a specific finding in those patients who had propranolol abruptly withdrawn. Patients who had propranolol maintained just prior to surgery (group IV) failed to demonstrate this postoperative rate-pressure product of arrhythmia increment. Catecholamines were not measured so it is not exactly known whether the postoperative rate-pressure product increments in this study are secondary as suggested by others<sup>33</sup> to increased catecholamine levels, adrenoceptor hypersensitivity, or both.

In this study the finding that those patients who had propranolol stopped just 10 hours prior to surgery and were not protected from marked increments in rate-pressure product during the operative (intubation) and postoperative period was surprising in light of the alleged prolonged pharmacodynamic half-life of propranolol which contrasts to its shorter pharmacokinetic half-life.<sup>34</sup> This might be explained by the

increased clearance of the drug during cardiopulmonary bypass and the heightened adrenergic state in the immediate postoperative period. Negligible plasma drug levels were found following cardiopulmonary bypass in both group III and IV patients reinforcing a need to maintain propranolol intravenously in the immediate postoperative period to protect against the postoperative hyperadrenergic state.<sup>34-35</sup>

There are important clinical implications of this study. First increased myocardial oxygen demands during intubation may be even more important than a compromised blood supply in causing ischemia. The finding of intubation-induced hypertension and tachycardia has been demonstrated in many studies, which emphasize the need to protect patients with beta-adrenergic blockade from this catecholamine-mediated phenomenon.<sup>36</sup> Moreover a propranolol withdrawal effect following abrupt premature discontinuation of the drug may further aggravate this phenomenon.<sup>37</sup> Many of the perioperative myocardial infarctions which have been observed with coronary bypass surgery<sup>38</sup> may relate to the intubation-related increase in rate-pressure product, an effect which usually persists for five minutes.<sup>3</sup> In this study five myocardial infarctions were seen in group II and group III patients vs. none in group IV patients.

Secondly, there is probably no need to give propranolol during the operative period. Halothane and enflurane are the general anesthetics most commonly used for coronary artery bypass surgery and like propranolol, are myocardial depressants (agents that will lower the oxygen demand of the heart).<sup>3</sup> These anesthetic drugs have been shown to decrease the activity of the sympathetic nervous system and to reduce the output of catecholamines by adrenergic nerve endings and the adrenal medulla. Direct effects on autonomic nerve terminals have not been demonstrated and there is no reason to believe nor any evidence to support the notion that halothane may act on adrenal receptors.<sup>39</sup> As demonstrated in this report patients in all four groups had similar low rate-pressure products after one hour of halothane anesthesia. The effects of propranolol and halothane are usually additive and not potentiated with the concentrations of halothane used in coronary artery surgery.<sup>40</sup>

Thirdly, the well-documented hyperadrenergic state in the early postoperative period<sup>3, 41</sup> may

explain the high incidence of hypertension and arrhythmias reported in this study.<sup>37-41</sup> Maintenance of propranolol given intravenously appears to blunt this stress reaction whereas premature propranolol withdrawal seems to aggravate it. The supraventricular arrhythmias appear to be catecholamine mediated since they all respond to intravenous propranolol therapy. Unlike propranolol the efficacy of digoxin in treating postoperative arrhythmias has not been demonstrated.<sup>39</sup>

Maintenance of myocardial oxygen demands at relatively low levels with propranolol might be especially important in the prebypass operative period for patients undergoing complete coronary artery revascularization. The demonstration that perioperative myocardial infarction often occurs in the period between anesthesia induction and onset of cardiopulmonary bypass emphasizes the need for myocardial protection during this most vulnerable period.<sup>40,41</sup> In the postbypass period myocardial oxygen demands should also be controlled especially in those patients who undergo incomplete coronary revascularization procedures where threatened myocardium may still remain or in noncardiac operative procedures for patients with angina pectoris where the entire myocardium may remain threatened.

The mortality rate of patients with angina pectoris undergoing elective noncardiac procedures has been reported to be three times higher than that of patients undergoing elective coronary revascularization procedures.<sup>42</sup> Proper anesthetic technique and careful hemodynamic monitoring are important for all patients with ischemic coronary artery disease who undergo either noncardiac or cardiac operations. In this study all the perioperative myocardial infarctions were seen in those patients who either had propranolol abruptly withdrawn or who never received the drug preoperatively.

Many of the newer beta adrenoceptor blocking agents (i.e., practolol, cardioselective pindolol, intrinsic sympathomimetic activity, alprenolol, labetalol, alpha and beta blocking activity) have been evaluated during surgical procedures and like propranolol were found to be well tolerated.<sup>33-41</sup> Since all the beta adrenoceptor blocking agents have similar effects on angina pectoris, arrhythmia, and hypertension, the danger of abrupt treatment withdrawal with these agents should parallel that seen with propranolol.

## Conclusions

1 Propranolol can safely be maintained just prior to coronary artery surgery in hemodynamically stable patients and can be safely resumed in the immediate postoperative period with no difficulty.

2 Propranolol blunts the profound increases in myocardial oxygen demand seen during intubation and postoperative periods. These increments appear to be catecholamine mediated and are unrelated to the renin-angiotensin system.

3 There is a demonstrable propranolol withdrawal effect when the drug is abruptly stopped 10 to 48 hours prior to coronary artery surgery which appears to aggravate the hyperadrenergic state seen during the intubation and postoperative periods.

4 There is a rapid clearance of propranolol during cardiopulmonary bypass with disappearance of the drug demonstrating the need to temporarily restart the drug in the immediate postoperative period where adrenergic tone is high.

5 There is a high incidence of supraventricular arrhythmias seen in patients where propranolol is abruptly withdrawn 10 to 48 hours prior to surgery. The arrhythmias are probably catecholamine mediated since they are prevented by propranolol prophylaxis and respond readily to treatment with propranolol.

6 The recognition of a propranolol withdrawal effect during cardiac surgery raises an even greater concern for those patients with chronic angina pectoris who are receiving propranolol prior to undergoing noncardiac surgical procedures and where the drug is abruptly stopped.

**Recommendations.** We strongly believe that with the proper indications for its use chronic therapy with propranolol should be continued in moderate doses to the time of surgery (we recommend half the usual dose be given orally 2 hours prior to surgery and restarting intravenous propranolol immediately postoperatively). Not only will this minimize the occurrence of complications of the patient's disease in the preoperative period but cardiovascular stability may actually be improved by the persistence of propranolol effects during anesthesia. The lower heart rate and blood pressure are favorable for minimizing myocardial oxygen demands and the incidence and severity of episodes of tachycardia and dysrhythmias are probably less in patients main-

tained on beta blockers up to the time of surgery.

Propranolol should not be abruptly withdrawn even as early as 10 hours prior to surgery. The question of gradual withdrawal of therapy prior to surgery has not been well resolved but in the absence of apparent complications from continued propranolol therapy there is little justification for even gradual withdrawal.

### Summary

In an attempt to resolve the controversy concerning propranolol therapy in patients undergoing coronary artery revascularization surgery 54 consecutive patients with stable angina pectoris receiving chronic propranolol therapy entered a randomized trial and were compared with 17 patients on no propranolol therapy (group I). The 54 patients were divided into three treatment groups in group II ( $n = 17$ ) propranolol was abruptly withdrawn 48 hours prior to surgery in group III ( $n = 18$ ) propranolol was abruptly withdrawn 10 hours prior to surgery in group IV ( $n = 19$ ) propranolol was maintained until the day of surgery half the usual dose was given 2 hours prior to surgery and intravenous propranolol was administered every four hours postoperatively. Patients in group II and III had significantly higher increases in the rate pressure product (RPP) during intubation and in the postoperative period compared to patients in groups I and IV. Group IV had the lowest increase in RPP during intubation and a significantly lower incidence of postoperative supraventricular arrhythmias. Patients abruptly withdrawn from propranolol at 10 or 48 hours preoperatively are more prone to increments in myocardial oxygen demands than those patients not treated with propranolol postoperatively or who were maintained on the drug. Plasma renin activity although lower in patients treated with propranolol (group IV) did not seem to play a role in the RPP increments seen. The increased sympathetic tone associated with intubation and the postoperative period most likely contribute to the increments in RPP and the increased incidence of arrhythmia. These data show that (1) propranolol may be given safely to patients at the time of coronary artery bypass and may be maintained postoperatively without a decrement in left ventricular performance (2) there is a rebound effect or increased sympathetic activity

in patients who have propranolol abruptly withdrawn 10 or 48 hours prior to surgery. This rebound effect causes a marked increase in myocardial oxygen demands during intubation and the postoperative period with an increased incidence of arrhythmias (3) Continuous propranolol treatment up until the time of surgery with maintenance of intravenous therapy in the immediate postoperative period provides protection against these complications (4) The data and implications can reasonably be expected to apply to propranolol treated patients with angina pectoris undergoing general anesthesia and non cardiac surgical procedures.

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## Measuring ventricular function after coronary bypass surgery

From the onset of the coronary bypass operation clinical investigators have reported improvement of ventricular function following operation with the conclusion that the observed changes were the result of the specific effect of the operation. Studies of exercise capability and more recently studies using sophisticated radionuclide techniques of measuring ventricular function have demonstrated with "statistical significance" an improvement following coronary bypass. Although most clinicians find an immediate and seemingly rational causal correlation between the operation and subsequent ventricular improvement, fitting with prior "clinical judgment" this correlation with its attendant conclusion is an unproven hypothesis. It may well be correct but needs testing lest it be wrong and lead to false conclusions. The conclusion that the operation is responsible for improvement rests on the exclusion of other factors that may also result in improvement. For centuries, clinicians initially have alleged benefit from almost all therapeutic innovations because of the association of patient improvement following the therapy. It is not enough to observe that patients improve following therapy—that happens with most therapies and often without or in spite of therapy. It is an anachronism of the clinical investigation paradigm that there often is no scientific testing to determine the specific factor responsible for improvement following therapy.

There has always been a tendency for clinicians to mistakenly equate objectivity of assessment with objective measurements. If a biological function can be measured by objective standards, such as weight, length, time or ejection fraction, the majority of clinicians assume that assessments based on such measurements are objective. For example it was alleged that because patients could walk up and down more steps following the Beck operation as compared to before the operation that this constituted "objective" evidence of improvement due to the operation. Although the measurements of steps were objective and no doubt accurate the assessment was not objective because no attention was paid to the many other factors that were involved in the longer exercise performance of those patients.

In addition to the specific effect of coronary bypass surgery, there are many other factors that may possibly contribute to or explain improvement in ventricular function. Those of which we are aware include the following:

1 The regression effect is usually overlooked in a assessment of therapy. Patients who have chronic illnesses go through cycles of variation of symptoms and disease. They are much more likely to seek medical help and a physician is much more likely to determine and note their status during clinical relapses (as is the case with a patient after bypass surgery) as at the period of remission. The effect of clinical relapse or of the net symptomatic period is such that many patients receiving therapy will otherwise have improved symptoms and hence improved function.

likely will improve spontaneously following periods of increased ischemia and attribution of improvement to an intervening therapy may be incorrect. Failure to account for this phenomenon produces an unwarranted bias in assessment of the therapy.

2 Patients receiving coronary bypass surgery almost always have a profound belief that this therapy is protective against myocardial infarction or death and many look upon the treatment as curative. It is axiomatic that powerful psychological factors influence physiologic functioning, and although we know very little about quantification of such factors it is clear that psychological factors are very important in exercise test results, and it is possible that they play a role in exercise ventricular function as well. Certainly any therapy that reduces anxiety, as does coronary bypass surgery, will produce profound symptomatic improvement on that basis alone. This fact is virtually never accounted for in evaluation of symptomatic results of bypass surgery. The non-specific effects of major surgical therapy are well demonstrated in patients with unsuccessful bypass operations (all grafts occluded) most of whom have improved ventricular function after operation. Patients who received the Beck, internal mammary artery ligation and Vineberg operation, also had improved ventricular function. Proper evaluation of bypass surgery must account for this important factor.

3 Physical conditioning is capable of improving ventricular function in patients with severe coronary artery disease even to the extent of reversing or eliminating decreased ejection fraction with exercise. If patients who have had coronary bypass surgery feel that they are sufficiently protected that they can embark upon exercise conditioning programs as is encouraged, this factor alone could improve ventricular function as compared to medically treated patients who do not change their life styles. Even though increased physical conditioning may be secondary to a psychological effect of surgery (as may be the case with cessation of smoking also) these are non-specific effects of the therapy and should be recognized as such. It is inaccurate and potentially misleading to assess bypass surgery without accounting for exercise conditioning before and during the evaluation period.

4 Perhaps the most important determinant of observed differences of ventricular function comparing operated and non-operated patients, is an inherent difference between the treatment and control groups. If the control group of patients is not selected by the same criteria used for selection of patients for coronary bypass surgery, the groups will be inherently different. Therefore observed differences noted at a later date due to different prognoses of the groups are not only possible but expected. There is much evidence that patients selected for coronary bypass surgery are inherently different from those selected not to have surgery. When surgical patients are compared to non-surgical patients an

most cases the comparison is invalid regardless of statistical analysis because of the inherent differences between the groups. The great majority of all studies of ventricular function following coronary bypass surgery suffer from this deficiency.

Another possible influencing factor well known but usually unheeded is the natural bias of investigators who have an interest in the outcome of studies. Quite aside from personal integrity if one stands to gain from a particular observation the likelihood of making that observation is enhanced. Clinical investigation is one of the few spheres of testing in which assessments are made by those who have a direct and personal interest in the outcome rather than by unbiased independent investigators.

The basic fallacy in most studies of ventricular function is the failure to provide an adequate control group. Proper controls do not ensure that the two groups are absolutely equal, and they are sometimes very difficult to obtain but without a valid control group for comparison there is no way to isolate the specific effect of the treatment under study from the many other factors that may influence the end result. It is far better that we utilize scientific methods even if it means that we must profess uncertainty about the causal relationship of therapy and observed changes than to deceive ourselves with uncontrolled studies that lead to false conclusions. In the absence of adequate controls, most clinical investigations provide a parody of scientific analysis and produce belief of unsupported hypotheses that frequently perpetuate worthless concepts or therapies.

Coronary bypass surgery may well improve left ventricular function or it may not; the studies to date are insufficient to provide accurate information. It is scientifically unacceptable to conclude that bypass surgery is the specific cause of ventricular functional improvement when so many other factors that can explain the observation are not even consid-

ered. We must be willing to say that although ventricular function appears to improve following bypass surgery we do not know what proportion if any of that improvement is due to the operation. Until we learn to admit of our lack of knowledge and adopt methods that are more accurate we will be bereft of that knowledge that we so forcefully proclaim.

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## The risks of intestinal bypass operations

Recently it has been determined that a 35 to 45-year old man with a weight excess of 100 pounds is ten to eleven times more likely to die than his normal weight counterpart. Most deaths were related to cardiovascular disease. Medical measures to produce weight loss had been notoriously unsuccessful justifying surgical approaches which promised lasting improvement. However, before recommending any of the various surgical procedures to treat obesity the limitations and hazards should be well understood.

The intestinal bypass has enjoyed increasing popularity and is still the most widely used operation. Interestingly the first patient so treated by Dr Kremen in Minneapolis is still alive 24 years later but has had a coronary occlusion—despite normal weight. This brings up the first question: Does the drastic decrease in serum triglyceride and cholesterol levels following this procedure prevent ischemic heart disease? There is evidence that HDL concentrations diminish as well and cholesterol content of arterial tissue actually rises. Thus

the lowering of blood lipids may not result in lessened atherogenesis.

Admittedly in addition to weight loss there are health benefits. Blood pressure is lowered. Blood sugar if elevated becomes normal in most patients. Pickwickian patients improve and the hazard of pulmonary embolism is lessened. However, actuarial data on the survival of bypass patients have not been published. Thus we don't know if this group will live longer than untreated obese subjects, but it has become abundantly clear that the intestinal bypass only rarely achieves normal weight plus good health. Obesity with its handicaps was traded off against a multitude of minor and major acute or chronic complications.

The long excluded bowel segment is equivalent to a huge blind loop and all the manifestations of a blind loop syndrome can be anticipated. Arthritis, vasculitis in various forms, skin lesions, and neurological defects have been described. Progressive damage involving the liver or the kidneys may occur



without subjective symptoms or clinically recognizable manifestations. Only sequential liver biopsies will reveal worsening fibrosis, but cirrhosis can be prevented by timely dismantling of the bypass. Damage to the kidneys is a much more problematic and treacherous complication. Biopsies had demonstrated extensive structural changes while kidney function tests had remained entirely normal. At least two mechanisms can cause renal injury. First, nearly all bypass patients develop hyperoxaluria and in close to half the patients oxalate crystals are deposited in tubules, causing focal lesions, fibrosis, and atrophy. The incidence of severe renal oxalosis is unknown. The rate of progression can be highly variable. Irreversible renal failure has occurred as early as three months, and as late as seven years after the operation.

Second, injurious immune complexes, related to bacterial overgrowth in the bypassed bowel, have been found to cause a glomerulopathy independent of the oxalate-induced damage. The clinical course of this type of interstitial nephritis has not been defined, but there are indications that functional impairment may ensue through this mechanism as well. The morphological picture ranges from a granulomatous nephritis to glomerular pathology indistinguishable from disseminated lupus erythematosus. While hepatic failure may be preventable with proper treatment, there is no evidence that the renal injury is avoidable. The great majority of bypass patients studied had variable degrees of renal damage.

There may be in excess of 80,000 bypass patients in the United States. The overall complication rate has been high

and several large centers have concluded that intestinal bypass operations are no longer a viable treatment modality. In fact, it would seem reasonable to advise bypass patients of the possible long range hazards. The suggestion might be made that the bypass can be dismantled and that a gastroplasty or gastric exclusion operation could be substituted in order to prevent recurrent weight gain. These operations are considerably safer since mechanical interference with food intake is the only effect.

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## Doctors, drugs, and compliance

As internists, our major therapeutic approach to patients with medical problems is the use of drugs. The success of our efforts is heavily dependent on the efficacy of the agents, effective preventing of drugs, the compliance of the patient in taking the drug, and the avoidance of adverse drug reactions. It should therefore be evident that to evaluate the success or failure of a drug regimen, one must know certain basic information: the name of the drug used, the dosage and directions given to the patient, and the names of other drugs being given concomitantly. In private practice settings, such information may be remembered between visits by the practitioner. Where multiple providers are caring for the same patient, as in group practices or hospital-based programs, the major means of communication of such information is the medical record.

In a recent study, the medical records of 100 patients followed in a hospital-based outpatient program were examined to determine if information relating to drugs was adequately documented. To do this, investigators independently reviewed the medical record and the prescription files of drugs actually dispensed to the patient. The medical record could then be evaluated for completeness and accuracy of drug names, dosage and directions. There was a discrepancy between the pharmacy files of drugs dispensed and the

medical chart in one or more of these items in 70% of the records. Drugs with a narrow therapeutic range such as anticoagulants, digoxin, antiarrhythmics, or chemotherapeutic agents, were no more accurately documented than were other agents. Where two or more drugs with a potential for significant drug interaction were being administered, one of the drugs was not named in the chart in 67% of the cases. For 40% of the patients receiving Warfarin and a potentially interacting drug, the chart failed to document one of the drugs. Forty-three patients received two or more drugs of the same therapeutic type including analgesics, sedatives, and diuretics. These duplications were not evident in the chart in 22 instances (51%).

When we assess the outcome of medical care provided in this country, we can no longer tout our advanced technology as a guarantee of success. The literature reveals that even common medical problems such as hypertension are frequently poorly managed and have unacceptable outcomes. If we are to make a significant impact on the health of a large number of patients by our interventions, we must correctly identify the health problem, implement an appropriate therapeutic regimen, and monitor the results of such therapy. The problem of patient compliance has received minimal amounts of attention. A variety of approaches have been tried

improve patient compliance in drug therapy by intervention of physicians, nurses, pharmacists, and other trained personnel. Many of these interventions are associated with element but often compliance returns to pre-intervention level upon withdrawal of the program.

Beneficial outcomes of therapy, however, depend not only on patient compliance but also on rational drug use and absence of adverse drug reactions and interactions whenever possible. This "physician compliance" has received far less attention and is most often focused on improving the physician's understanding of the pharmacology and appropriate use of specific drugs. Such cognitive knowledge will have little effect on patient outcomes if the practitioner caring for the patient does not have accurate information on what drugs the patient is receiving. The added dimension of complete and accurate documentation must be considered an integral part of programs to improve outcomes of our therapeutic efforts.

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## The Constitution

The Constitution of the United States is probably the greatest document ever written by man. That document could not have been written today!

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## Failure of prophylaxis for bacterial endocarditis American Heart Association Registry

To the Editor

The American Heart Association (AHA) recognizes that its current recommendations for antibiotic prophylaxis are necessarily empirical. This situation has arisen because important clinical information on the efficacy of antibiotic prophylaxis of bacterial endocarditis is lacking. The present recommendations are therefore based upon secondary sources of information such as the relative propensity of various procedures to cause bacteremia, *in vitro* studies of bacteria recovered from the blood, the effect of antibiotics on bacteremias, the susceptibility of various heart lesions to infection, anecdotal case reports, and the study of experimental models.

Although over 30 individual cases of apparent prophylaxis failure have been recorded in the literature, many of our colleagues have rightly pointed out that the evidence indicating that a significant number of prophylaxis failures actually occur is inconclusive. This question is of considerable medical and medico-legal importance because of the frequency with which measures to prevent endocarditis are called for and because of the serious consequences of failure to prevent the disease.

In an attempt to accumulate useful epidemiologic data, the AHA Committee has established a Registry to record cases of apparent failure of antibiotic prophylaxis of bacterial endocarditis. We are now soliciting case reports. Notification may be made on a simple pre-printed postcard which will require only identification of the patient and the name, address, and telephone number of the person referring the case. These postcards will be made available to physicians and dentists and to any other person or organization requesting them from the AHA or from one of us. Alternatively, a case may be reported directly to one of us at the address or telephone number listed below. After notification, one of us will follow up with a telephone call in order to gather sufficient information to evaluate the case. All such information will be confidential.

Although there are obvious disadvantages to any retrospective evaluation, this is the practical impossibility of conducting a prospective trial of different modes of prophylaxis used to seek alternative means of gathering data. We hope that a useful body of information may be accumulated which may utilize future recommendations for pro-

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## Physical training in patients with coronary artery disease

To the Editor

Greenberg and associates dismiss the marathon runner's immunity to atherosclerosis with a sentence containing glaring errors. Others have refuted this as an exaggerated claim by documenting cases of fatal myocardial infarction in marathon runners. They cite the report from South Africa which contains detailed clinical data on six marathoners who developed apparent heart attacks. However, only one runner died. There was no autopsy; however, DeWitt reviewed the ECG and found it consistent with heart stroke. This runner had been taking long training runs, up to 40 miles in length during the hot running season. The remaining five runners were alive and running at the time of publication. Angiograms were available on four. The runner with the most severe abnormalities on angiogram subsequently completed a 100-mile race. Thus, the authors did not refute the concept of the marathoner's immunity to atherosclerosis since there was no evidence of either death or disability due to this disease.

I have followed 131 cardiac patients for 500 patient-years after they trained up to marathon distance in formal rehabilitation programs. These include 49 with myocardial infarction and 19 with coronary bypass. Follow-up shows that 14 are alive and running. Of the five who died, only one showed progressive atherosclerosis. This man chewed tobacco and swallowed all the juice from three boxes of chewing tobacco a week. I attributed his vascular lesion to the angiotoxic material in tobacco juice, and I still consider the marathoner immune to atherosclerosis.

Atherosclerosis is the major cause of death in physicians.

Greenberg's associates. Therefore I vigorously encourage all physicians to conform to a life style which allows them to at least walk the 42 km marathon distance share in this protection! Interested physicians are urged to the ranks of the other marathoning professionals in the Medical Joggers Association.

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#### To the Editor

Bassler<sup>5</sup> has asserted that marathon running (the ability to 49 kilometers) imparts immunity from atherosclerosis. The report by Noakes and others<sup>2</sup> contains case reports of infarction in six such marathon runners including one fatal infarction. The fatal infarction occurred in a 35-year-old man who for at least one month prior to his death severe exertional chest pain while running. In spite of a doctor's advice and in spite of having to stop running on occasions because of chest pain he continued to run and refused medical attention. On the day of his death he developed severe chest pain with radiation to the left arm associated with shortness of breath. He died shortly after admission to the Intensive Care Unit. An electrocardiogram acute inferior subendocardial ischemia. As he had not been running on the day of his death, it is unlikely that neither the electrocardiographic changes or the runner's death were due to heat stroke. It is interesting that all six runners reported by Noakes ignored warning symptoms and runners prior to their myocardial infarction.

A more recent report by Noakes and co-workers<sup>3</sup> provides autopsy evidence of atherosclerosis in four additional marathon runners. One of these runners died during a 24 km race. Another runner with a previous inferior wall infarction and unstable angina died while awaiting bypass surgery. This second athlete had angiographically proven progression of his coronary atherosclerosis over a two year period during which he continued marathon running.

In evaluating the protective effect of marathon running on coronary deaths other factors such as diet, smoking habits and self-selection must be considered. The incidence of fatal myocardial infarction in young, thin, non-smoking males is extremely low. Milvy<sup>4</sup> has estimated that even if marathon running offered no protection at all, one would only expect

one or at most two fatal myocardial infarctions per year in this group. Thus, it would be difficult to prove that marathon running conferred immunity from coronary deaths.

For the non-marathon runner there is even less controversy about coronary deaths. Even Bassler<sup>5</sup> reports that fatal myocardial infarctions can occur in non-marathon runners. Two of these deaths reported by Bassler occurred in athletes who had won Olympic gold medals and had set world track records.

The purpose of our review was to discuss the physiologic effects of exercise in patients with coronary artery disease and its role in treatment. Exercise improves cardiovascular fitness and may possibly be beneficial in the prevention of coronary heart disease. Claims of total immunity from atherosclerosis in a highly selected group do not substitute for careful epidemiologic studies. Furthermore, these claims may dissuade athletes and joggers from responding appropriately to warning symptoms of impending coronary events.

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#### Asystole after pacemaker placement

##### To the Editor

A recent Letter to the Editor (*AM HEART J* 87:815 1979) described carotid sinus hypersensitivity resulting in cardiac asystole and hypotension. The asystole was treated by cardiac pacemaker but significant hypotension and resulting symptoms persisted. We recently reported a similar case in which the symptoms and hypotension which persisted after successful cardiac pacemaker placement were relieved by bilateral surgical denervation of the carotid sinuses.

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**Clinical Phonocardiography and External Pulse Recording** By Morton E. Tavel M.D. Chicago and London 1978 Year Book Medical Publishers Inc. 391 pages

This is a good book which has been well received. The pulse recordings and phonocardiograms are thought provoking. They stimulate interest and understanding of the mechanical and physiologic events of the cardiac cycle. The discussions are interesting, some of which this reviewer either does not understand or accept. For example, the author on pages 122 and 123 states that when the third and fourth heart sounds constitute a single sound this is termed a summation gallop. This reviewer has always thought that the cadence of a galloping horse constituted a gallop rhythm of the heart sounds and not merely a single sound. This needs clarification. The cadence of a gallop rhythm is heard on auscultation and is difficult to appreciate readily from a recording. Regardless of such details in clinical cardiology, the recordings are good and the mechanical and hemodynamic significance of the components of the various tracings are of extreme value to undergraduate students, housestaff, and physicians who are in training in cardiology. This is a book that requires critical and thoughtful reading. This is a good book—a book worth owning.

**The Clinical Recognition of Congenital Heart Disease** By Joseph K. Perloff M.D. Philadelphia 1978 W.B. Saunders Company 781 pages Price \$43.50

This second edition of Perloff's monograph written in textbook format on congenital heart disease is an excellent review of the subject. The text is written for clinicians with special procedures such as cardiac catheterization included for those who engage in this procedure as well as for clinicians who must depend on the data obtained by the various special procedures. It is impossible to review this entire book critically. However, it is interesting to find a chapter on primary pulmonary hypertension in a book on congenital heart disease. Surely this is an important disease in all age groups, but is it congenital? This book is a very good single source of information for clinicians on congenital heart disease. It is a book worth owning for study and for reference.

**Understanding Cardiology** By Hywel Davies M.A. D.M. F.R.C.P., and William P. Nelson M.D. Boston and London, 1978 Butterworth & Co. Ltd. 424 pages Price \$39.95

This is a practice book on clinical cardiology. The authors have introduced recordings of hemodynamic phenomena into bedside clinical cardiology. They fail, however, to emphasize adequately the limited need for hemodynamic phonocardiographic or other recordings in the daily practice of cardiology or general medicine. There is a need to learn when special procedures are necessary for the actual care of patients. The illustrations are numerous and excellent. The diseases discussed are fairly complete and the presentations are lucid and brief. The authors have summarized for the beginner pertinent information. This book is intended for beginners in medicine and cardiology but must be supplemented by much more extensive reading and study. The bibliographies are good but far from adequate. This is a good book for clinicians, especially undergraduate students, housestaff, and family physicians. The chapters on electrocardiography, arrhythmias, and echocardiography are particularly inadequate and would require more extensive study. The presentations of these important aspects of cardiology are somewhat superficial. Readers will need to supplement these subjects in greater detail. This is a very brief summary of a large subject: clinical cardiology.

**Heart Disease in Infancy and Childhood** By John D. Keith, Richard D. Rowe and Peter Vlad. New York 1978 Macmillan Publishing Company Inc. 1083 pages Price \$50.00

This is an outstanding book on heart disease in infants and children. The first two editions were a great success and were used worldwide. The third edition brings the subject up to date. For example, the use of echocardiography and His bundle recordings are now thoroughly discussed. The contributors are numerous and the respective contributions are nicely integrated with that of the others. This book is complete enough to provide a thorough knowledge of clinical cardiology in infants and children. This is an excellent book which should be in the library of all pediatricians and all cardiologists, including adult cardiologists.

## Books received

**Rehabilitation After Myocardial Infarction Unit 2** By Rebecca M. Garcia R.N. MSN. New York 1978 Appleton-Century-Crofts, Inc. 3 pages Price \$5.00

**Arterial Hypertension** Report of WHO Expert Committee. Geneva 1978 World Health Organization 4 pages

**Drugs, Lipid Metabolism and Atherosclerosis** Edited by David Kritchevsky, Rodolfo Faletti, and William L. Hines. New York 1978 Plenum Publishing Co. 413 pages Price \$22.00

**Trauma to the Heart and Great Vessels** By Panagiotis Symbas M.D., New York 1978 Grune & Stratton Inc. 20 pages Price \$22.50

**Cardiovascular Medicine Controversies** Edited by Cline Wood. New York 1978 Grune & Stratton Inc. 83 pages Price \$10.25

**Att VIII Congresso Nazionale** Catania 13 Aprile 1977. Edited with the collaboration of Crispa F. Berger. Rome 1977 Luigi Pozzi Publisher 859 pages.

## Cardiac and Pulmonary Imaging

The Department of Radiology and the Office of Continuing Education of the University of California San Diego School of Medicine are offering a course entitled "Cardiac and Pulmonary Imaging," to be held on February 8 through 10 1980 in San Diego. The Program Director is Michael J. Kelley, MD, and the guest faculty includes Arthur D. Hagen, MD, Walter L. Henry, MD, Martin J. Lipton, MD, Charles L. Putman, MD, and Lewis Wexler, MD. Participating faculty of the University of California will include Naomi P. Alazraki, MD, William L. Ashburn, MD, Joseph J. Bookstein, MD, Marc N. Coel, MD, David S. Feigin, MD, John V. Forrest, MD, Paul J. Friedman, MD, Victor F. Froelicher, MD, Charles B. Higgins, MD, Michael J. Kelley, MD, Kenneth M. Moser, MD, Ralph Shabetai, MD, and Andrew T. Taylor, Jr., MD. Fee for the course is \$200 and 19 hours of Category I AMA credit will be given. For further information contact Mary J. Ryals, Radiology, P.O. Box 330, La Jolla, Calif. 92038. Telephone (714) 459-9187.

## Dr. Heinz Karger Prize 1979

The Dr. Heinz Karger Prize, awarded every year in memory of the well-known Basel publisher for an outstanding scientific work, has been awarded in 1979 to Dr. Louis Tobian, USA, for his paper "Evidence for Na-retaining humoral agents and vasoconstrictor humoral agents in hypertension-prone Dahl S rats. Prevention of NaCl-induced hypertension in Dahl S rats with thiazide."

For 1980 the Dr. Heinz Karger Memorial Foundation invites the submission of papers on the topic: "Antibodies with intrinsic biological activity." The paper must be an original research work and must reach the publisher no later than February 28, 1980.

For 1981 the Foundation invites the submission of original research papers on the subject: "Intestinal absorption of peptides." Papers must reach the publisher no later than February 28, 1981.

Manuscripts shall not exceed 20 typewritten pages including illustrations, tables and bibliography. Manuscripts must be typewritten on one side only, double-spaced, submitted in quadruplicate and must be marked. Competition in accordance with the instructions contained in "Rules for the Preparation of Manuscripts." This leaflet can be obtained free of charge from the publishers. Papers may be written in English, French, or German. Papers should be mailed well within the deadline date to: S. Karger AG, Arnold Bocklinstrasse 25, CH-4011 BASEL, Switzerland.

The winning paper for each year will be published in English in one of the Karger journals. The award will be 7,000 Swiss francs. The Council of the Foundation will judge the papers and will confer the prizes.

## Seminar on Cardiovascular Epidemiology and Prevention

The Council on Epidemiology and Prevention of the International Society and Federation of Cardiology announces its thirteenth Ten Day International Teaching Seminar on Car-

diovascular Epidemiology and Prevention to be held near Leningrad, Lituania, USSR, on August 16 through 29, 1980. Approximately 30 Fellows will be selected. Nominees should normally be at the postgraduate level with some residency training or its equivalent and be interested in cardiovascular disease epidemiology. Partial assistance with travel costs may be available for accepted Fellows. A room and board are provided without cost. Fluency in English is an absolute essential. Applications including (1) a letter of nomination by the chief of the nominee's department or institution, (2) a personal letter of application from the nominee, and (3) the applicant's curriculum vitae should be received before March 15, 1980 by Rose Stamler, Seminar Coordinator, 303 F. Chicago Ave., Room 1-615, Chicago, Ill. 60611.

## University of Arizona Travel Study Program

Two separate sessions of a seminar entitled "Recognition and Management of the Stroke-Prone Patient" will be offered this spring. The first will be held on March 10 through 22 at The Mark Resort, Vail, Colorado. The second session will take place on May 3 through 9 at Frenchman's Reef, St. Thomas, U.S. Virgin Islands. Each session will carry 20 hours of approved Category I AMA credit. For registration materials and further information contact: Office of Continuing Medical Education, Attn: Faith Carlini, University of Arizona Health Sciences Center, Tucson, Ariz. 85724. Telephone: (602) 626-6173.

## Atherosclerosis in nonhuman primates

In conjunction with the VIIIth Congress of the International Primatological Society, scheduled for July 7 through 12, 1980 in Florence, Italy, a symposium entitled "Regression of Atherosclerosis in Nonhuman Primates" to be held on July 5 is being organized. Persons who wish to present 10-minute research papers related to the symposium topic are invited to submit four copies of a 300 word abstract to: M. H. Malinow, MD, Oregon Regional Primate Research Center, 500 N.W. 185th Ave., Beaverton, Oregon 97006, U.S.A. Abstracts must be postmarked no later than February 28, 1980 and must include title page with the author's name, title position and mailing address.

## Nuclear Medicine Course

The Department of Radiology and the Office of Continuing Education of the University of California San Diego School of Medicine are offering a course entitled "Cardiovascular Nuclear Imaging" to be held on February 6 and 7, 1980 in San Diego. The Program Director is William L. Ashburn, MD, and the guest faculty includes David L. Gilday, MD, and Glen W. Hamilton, MD. Participating faculty of the University of California will include Naomi P. Alazraki, MD, William L. Ashburn, MD, Victor F. Froelicher, MD, Samuel E. Halpern, MD, Kenneth M. Moser, MD, Robert A. Slutsky, MD, Andrew T. Taylor, Jr., MD, and John V.

## *Announcements*

Verba Ph.D. Fee for the course = \$200 and 11½ hours of Category I CME credit will be given. For further information, contact Mary J. Ryals, Radiology, P.O. Box 2305, La Jolla, Calif. 92038. Telephone (714) 459-9787.

### **HLA System and Clinical Medicine**

A symposium entitled "The Relevance of the HLA System and Clinical Medicine" will be presented at the Hilton Hotel, San Diego, California, on March 15 and 16, 1980. The sympo-

sium is designed to update current information related to the HLA system and aspects of clinical medicine. A significant association has been demonstrated between HLA antigens and various diseases. The symposium will emphasize the importance of HLA testing in transplantation, paternity testing, and diagnosing various diseases. Fourteen hours of AMA/CMA credit will be available. For further information, contact Edith Bookstein, Program Assistant, University of California at San Diego, Office of Continuing Education, M-017, La Jolla, Calif. 92093. Telephone (714) 457-3734.

## Editorial

### From heart to brain the new definitions of death

Peter McL Black MD PhD

Boston Mass

In our society, physicians are generally responsible for declaring a person dead they usually require cessation of cardiorespiratory activity to make this declaration. Recent social and medical developments however have significantly changed both the concept of death and the criteria for its pronouncement. Instead of considering the heart as central to the determination of death, some physicians are now using death of the brain as adequate for death despite continued cardiac function.

It does seem that death of the brain is an important item even in traditional cardiac declarations of death. If someone's heart dies but his brain can be kept alive by an artificial heart or by a transplanted one, he is not considered dead just because his own heart no longer functions. If his heart stops every attempt is made at resuscitation because of the possibility that his brain might be kept perfused while his cardiac arrest is rectified. Now that physicians can keep the heart and lungs working even with a brain that has been destroyed, it is predictable that explicit attention be paid to death of the brain as an adequate criterion for death in general.

The concept that death is in fact brain death is being increasingly accepted in the United States. This is reflected in our courts and our lawmaking

bodies as well as in medical practice. The National Conference of Commissioners on Uniform State Laws for example has recently approved the Uniform Brain Death Act. This proposal states

For medical and legal purposes, an individual with irreversible cessation of functioning of the brain including the brain stem is dead. Determinations of death under this act shall be made in accordance with reasonable medical standards.

This is a proposal to be placed before state legislatures to achieve a uniform standard for the declaration of death. At least 18 states have already passed some kind of brain death legislation and several courtroom decisions have also made it clear that brain death is considered an adequate criterion for death in many jurisdictions.

In most cases the physician has to deal with this changing definition of death makes little difference. The prolonged absence of respiration and circulation that allows a diagnosis of death in most cases today is presumptive evidence of brain death as well since the heart is more resistant to anoxia and failed circulation than is the brain. However there are some cases in which the brain will have suffered widespread irreversible damage although the heart still beats. It is these situations that brain death criteria were intended to cover emergency situations by none of them can one declare a person dead until attempts at cardiac resuscitation

From the Heart Lung Service Massachusetts General Hospital Boston Mass

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They are all formulated to deal with some period of continued cardiac activity without apparent brain activity in a patient requiring respiratory support

### Criteria for brain death

Several approaches have been advocated to establishing brain death criteria. They have as a common goal the diagnosis of irreversible widespread brain destruction. Such destruction may be demonstrated pathologically or may be implied from a failure of bodily survival despite all treatment after criteria have been fulfilled. Some criteria require only physical examination in the appropriate setting; others require one or more isoelectric electroencephalograms (EEG's) as well; still others recommend a demonstration that all cerebral circulation has ceased.

Certain physical findings are a part of all criteria. These include absence of brain stem reflexes, spontaneous respiration and coordinated movement in the appropriate setting. Other items may vary; there may be reflex withdrawal of an arm or leg, which indicates only spinal cord activity. Pupils need not be widely dilated but must be fixed to light. The time interval required to establish these findings may vary.

In 1976 a conference of the Royal Colleges and Medical Faculties of Great Britain stated that physical examination in the correct setting was enough to establish brain death. These criteria require certain preconditions to be fulfilled and appropriate examinations to be completed. The preconditions are the exclusion of drug overdose, hypothermia, or metabolic disturbance as possible causes and the requirement that the patient be maintained by a respirator. The appropriate examination is that of brain stem function: pupils should be fixed to bright light; there should be no gag reflex or facial movements; and there should be no breathing despite a pCO<sub>2</sub> above the level required for respiratory stimulation. These criteria explicitly include any requirement for an EEG, establish that a neurologist is only necessary if the diagnosis is in doubt and leave the time interval variable depending on the cause of brain death.

The so-called Hall and Jennett criteria are based on physical examination as well. They make provision for an EEG as being "of great confidence" but the major requirements are the same as for the first set of criteria.

including absence of respiratory effort. They differ from the British criteria in requiring a 24 hour period in which there can be no change in the findings.

The committee of the American Neurological Association to study brain death has incorporated a blood flow technique into their recommendations. They suggest that one of two methods can be used to make the diagnosis. One method is to demonstrate intracranial circulatory arrest for 30 minutes. This approach, widely used in Europe, has also recently been proposed by a collaborative study group here. Theoretically, the brain cannot survive 30 minutes without blood flow. Practically, several studies have demonstrated that widespread destruction follows such an interval. The demonstration of failure of circulation to the brain may therefore be an important method of establishing brain death. Normally, this demonstration has been done by angiography requiring transcranial catheterization in an angiogram suite. New radio-isotope techniques, however, may make it possible to use this criterion more conveniently in any hospital with a nuclear medicine department.

In the situation where an attempt is not made to show intracranial circulatory arrest, there is a more complicated procedure proposed by the committee of the American Neurological Association. For this option, several items are necessary. There can be no pupil response to bright light, no movement of the eyes when twenty cc. of ice water is instilled into either ear, no gag or corneal reflex or any other cranial nerve reflex, and no decerebrate or decorticate posturing. One EEG showing electrocerebral silence is "strongly recommended." There must be no spontaneous respiration. Perhaps most important, the patient must be observed for long enough (minimally 12 hours, perhaps as long as 72 hours) to a sure that drug intoxication, metabolic and other reversible abnormalities are not responsible for the neurological findings.

These criteria are the most recent attempt to develop broadly acceptable guidelines for brain death within the United States. They have been approved by the major neurological and neurosurgical organizations in this country, while presenting explicit tests, they also allow for variation depending on the circumstance. The variable time interval, the option of a single blood flow determination and the recommended but not

required EEG represent flexibility while still assuring that no recovery will be possible

### Goals of brain death criteria

The present diversity of criteria in brain death may be disconcerting to some physicians. It is in part a result of historical development which has occurred on two levels. The first is the philosophical and social—the acceptance of the idea that death of the brain is death of the person. This concept must be acceptable to a wide spectrum of society to provide impetus for work on the second level. It has however been increasingly accepted in the United States as the Uniform Brain Death Act exemplifies.

The second level is deciding what will be adequate evidence of a dead brain. This is a medical concern primarily and legislators and judges have left it for physicians to decide. However it is not an easy matter. The criteria adopted may reflect the goals of the adopters.

Consider for example the British criteria. These appear to have been developed primarily to achieve agreement for practical purposes throughout Britain. The work of the courts of transplant teams and of practicing physicians was made more difficult by uncertainty in this area. A uniform simple set of rules was therefore drafted which required nothing more than physical examination.

This approach may not allow for technological progress in such areas as blood flow determination. It has an arbitrary quality that may be distasteful to some. Perhaps most important it has been very difficult to achieve similar consensus in the United States.

There are therefore other goals than pragmatic agreement that brain death criteria might aim for. They might for example try to predict the pathological findings of a dead brain at postmortem. However this goal has also been difficult to achieve. There is significant disagreement about how much brain destruction is enough to qualify as a dead brain and the differences between changes occurring before and after cardiac arrest have not always been easy to define.

Many physicians have therefore used a third approach to guide the development of brain death criteria. This is the goal of predicting no survivors once criteria have been met. This has been done best for the Harvard criteria from published data a few weeks at most is the maximum time that

cardiac function continues. The reason for this is still unclear presumably it indicates a relationship between cardiovascular control and the brain stem that has not yet been clarified. By whatever mechanism however it appears that irreversible hypotension and cardiac arrest follow inevitably upon the fulfillment of the Harvard criteria.

For other proposed criteria the situation has not been quite as well established. The criteria of the collaborative study group which resemble those of the American Neurological Association guaranteed cardiac arrest within 12 weeks of brain death. These criteria are considerably broader in scope than the Harvard criteria yet still seem reliable in guaranteeing failure of survival.

It does appear that no one who fits present criteria for brain death will survive it all despite everything that can be done. Let alone some day recover neurological function. Brain death is quite different from a state of perpetual coma primarily in failure of respiratory drive and absence of all brain stem function. It is a state approaching cardiac death so closely that it seems reasonable to redefine death to include it.

It is an important task however to develop criteria for its determination that will be acceptable throughout the United States while allowing for change with advancing knowledge. The criteria proposed by the American Neurological Association appear to be the most significant recent contribution to this task. If continued testing demonstrates that they preclude survival despite all therapy, these criteria may become the standard for brain death within the United States.

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# The effects of atropine administered with standard syringe and a self-injector device

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Whether or not to employ atropine during the course of myocardial infarction has become a matter of some controversy in recent years.<sup>1-10</sup> The value of the drug is based on the presumption that bradycardia may induce ventricular arrhythmias and decrease cardiac output during acute myocardial infarction. Judicious increase in heart rate, it is thought, might prevent potentially fatal ventricular fibrillation from developing and increase perfusion of vital organs in particular the myocardium.

Opposition to the use of atropine in myocardial infarction has been supported by findings in dogs with experimentally created ischemia that increases in heart rate lower the fibrillation threshold and enhance the tendency for dangerous ventricular arrhythmias to arise.<sup>3-5</sup> Furthermore, vagotonia appears to have a protective effect in some experimental models.<sup>6</sup> Examples in man of increased ventricular irritability, ischemia, and hypotension arising after the administration of atropine during myocardial infarction have also tempered the unqualified enthusiasm for the use of this drug during an acute coronary event.

The need for the drug in particular cases, however, is not disputed. The hypotensive patient

with sinus bradycardia or junctional rhythm and/or A-V nodal block induced by vagotonia certainly appears to benefit by an appropriate increase in heart rate. At this writing there is no widely accepted consensus about how often and how generally atropine should be administered during an acute myocardial infarction.

Administration of the drug by intravenous injection is the favored technique in order to produce rapid onset of action and assure absorption. However, this method is not always appropriate. An intravenous line may not be in place or proper infusion equipment may not be available outside the hospital. Intravenous administration of the drug can be difficult for untrained personnel and even for skilled workers in the acute situation where vasoconstriction is present. In these particular instances where atropine may be needed and the intravenous administration cannot be carried out, a self-injection device with relatively rapid onset of drug effect could be useful.<sup>11-13</sup> One such device is the Atropen which delivers 2 mg of atropine in a citrate buffer intramuscularly. In this report we present the results of a study conducted in healthy volunteers to evaluate the effectiveness of this device in accelerating heart rate and to compare its properties with those of more accepted methods of administering atropine.

## Methods

Atropen is a spring loaded cylindrical device which contains 1.67 mg atropine base (equivalent to 2.0 mg atropine sulfate) in 0.7 ml of citrate

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Reprint request: Dr. John A. Kastor, Chief Cardiology, Hospital of the University of Pennsylvania, Philadelphia, Pa. 19104.

Developed by Surveil Technology, Inc., Bethesda, Md.

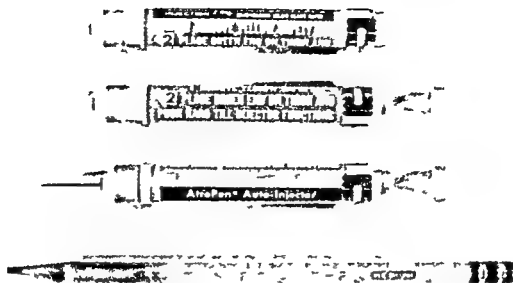


Fig 1 The Atropen device is illustrated as provided (top example) after removal of the safety cap (second example) and after extension of the needle (third example)

Table 1 Significance among different methods of administering atropine

	Resting rate	Peak rate	Time to 5" rate increase	Time to peak rate	Duration of rate increase
IV versus sulfate IM	N.S	N.S	< .001	< .001	< .001
IV versus citrate IM	N.S	N.S	< .001	< .001	< .05
IV versus Atropen	N.S	N.S	< .001	< .001	< .025
Sulfate IM versus citrate IM	N.S	N.S	< .005	< .05	N.S
Sulfate IM versus Atropen	N.S	N.S	< .001	< .001	N.S
Citrate IM versus Atropen	N.S	N.S	< .001	< .01	N.S

buffer solution (pH 4.3) (Fig 1) When the safety cap is removed and the instrument is pressed against a muscle mass preferably the quadriceps femoris of the thigh the spring mechanism is automatically released rapidly extending the needle to a tissue depth of  $\frac{1}{8}$  inch within 4 msec. Injection of the contents of the Atropen is completed in 260 msec. (Data on file with Survival Technology Inc. Bethesda Md.) Atropine base in citrate buffer is used in preference to atropine sulfate because of its greater stability when stored in the Atropen device.

Fifteen healthy volunteers ranging in age from 21 to 35 years served as subjects. None had a history of cardiovascular or autonomic nervous system disease, urinary retention or glaucoma.

There were 12 women and three men. Their average weight was 130 pounds with a range of 108 to 170 pounds. None had taken drugs, coffee, tea, or sodas or had smoked cigarettes in the 12 hour period before each study trial. Informed consent was obtained from each subject.

Each volunteer received four injections administered in a randomized sequence with one injection on each of four successive days. Injection conditions were defined as follows: (a) 10 ml solution containing 10 mg atropine sulfate (0.835 mg atropine base) injected intravenously with a conventional syringe; (b) 20 ml solution containing 20 mg atropine sulfate (1.67 atropine base) injected intramuscularly with a conventional syringe; (c) 20 ml solution containing 1

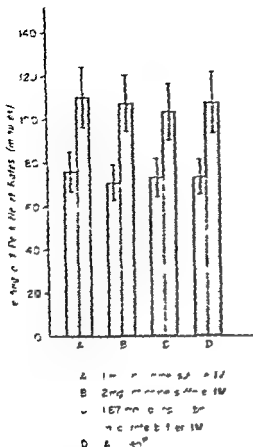


Fig 2. Graph represents one of the effects of a rapid on heart rate.

a ropine base in a citrate buffer solution (as contained in Atropen) injected intramuscularly with a conventional syringe (d) Atropen injection containing 1.67 mg atropine base in a citrate buffer solution. Intravenous injections were made into an antecubital vein and intramuscular injections were made into the anterior surface of the thigh. The intramuscular dosage was selected as twice the intravenous dose most often used in coronary care units on the assumption that the total effects on heart rate would be similar.

All subjects were studied in the supine position in a quiet room. Following a 20-minute rest period before each injection trial blood pressure (arm cuff) and radial pulse rates were recorded at two-minute intervals until both were stable for at least ten minutes. The injection was then completed and continuous electrocardiographic records were made during the first ten minutes of each trial to permit precise determination of changes in heart rate during the period. Pulse rate was measured every minute for the first ten minutes, then every three minutes for the next ten minutes, then every two minutes for the next ten minutes.

Peripheral blood pressure was measured every ten minutes throughout the trial.

When the rhythm was stable the heart rate was determined at 15-second intervals from the electrocardiographic strip by measurement of three consecutive R-R intervals. In the presence of sinus arrhythmia the rate was computed as an average from three randomly selected groups of three R-R intervals.

After the completion of each injection, the responses for heart rate versus time and for pressure were determined for each trial in every patient. The following characteristics of the heart rate response produced by each injection modality were studied: (1) resting heart rate (2) peak heart rate (3) time to onset of cardioacceleration (defined as a heart rate increase of greater than or equal to 5% above the resting heart rate) (4) time to peak heart rate (5) duration of heart rate increase above resting heart rate.

Subjects were questioned about side effects experienced during each study period. Many of the subjects were nurses and consequently were familiar with some of the side effects of atropine before the study began.

Statistical significance of the results was tested by Student's *t*-test and all data were expressed as mean  $\pm$  one standard deviation.

## Results

**Changes in heart rate.** The heart rate for each of the subjects increased significantly when atropine was administered regardless of the technique employed (Fig 2, Table 1). The cardioacceleration developed from mean control rates, which were similar and not significantly different among the four modalities of administration to peak rates which were also similar and not significantly different among the four modalities. 1 mg atropine sulfate intravenously—values from 75  $\pm$  6 beats/minute control to 110  $\pm$  14 beats/minute after the drug; 2 mg atropine sulfate intramuscularly—values from 71  $\pm$  8 beats/minute control to 107  $\pm$  13 beats/minute after the drug; 1.67 mg atropine base in citrate buffer intramuscularly—values from 73  $\pm$  9 beats/minute control to 103  $\pm$  13 beats/minute after the drug; Atropen—values from 73  $\pm$  8 beats/minute control to 107  $\pm$  4 beats/minute after the drug.

Intravenously administered atropine sulfate produced the most rapid onset of action (recognized by  $\geq 75\%$  increase in heart rate)  $0.6 \pm 0.4$

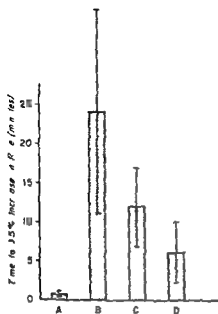


Fig 3 Graphic representation of the speed by which atropine increased heart rate For A B C D code see Fig 2

minute and this time was significantly shorter than for each of the other three modalities (Fig 3 Table I). Atropen produced significantly quicker onset of cardioacceleration  $6 \pm 4$  minute than did intramuscular atropine sulfate  $24 \pm 13$   $p < .001$  or intramuscular atropine in citrate buffer  $12 \pm 5$  minute  $p < .001$ .

The time to peak heart rate was significantly different among each of the four modalities when compared with each of the others (Fig 4 Table I). The intravenous method produced the most rapid increase to peak heart rate  $5 \pm 5$  minute. Atropen was second most rapid at  $26 \pm 13$  minute. atropine in citrate buffer intramuscularly followed at  $40 \pm 15$  minute and atropine sulfate intramuscularly produced the slowest response  $56 \pm 20$  minutes.

The duration of heart rate increase was significantly shorter when produced by intravenous administration and compared with each of the intramuscular methods (Fig 4 Table I). intravenous atropine  $62 \pm 34$  minute intramuscular atropine sulfate  $100 \pm 27$  minute intramuscular atropine in citrate base  $90 \pm 12$  minute Atropen  $98 \pm 18$  minute. Among the three intramuscular techniques the differences for duration of heart rate increase were not significant.

**Cardiodeceleration.** Initial transient cardiac slowing was detected in only three subjects after intravenous atropine whereas transient slowing

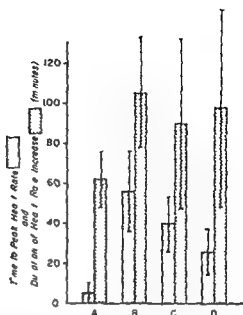


Fig 4 Graphic representation of the time to peak heart rate and duration of heart rate increase produced by atropine For A B C D code see Fig 2

was noted in ten subjects after Atropen and in nine after intramuscular atropine citrate and atropine sulfate. Slowing of the heart rate did not occur after any injection in four of the 15 subjects. The occurrence of sinus nodal slowing did not correlate with weight or the mean resting heart rate of the subjects.

**Blood pressure.** Both systolic and diastolic blood pressures rose following atropine but the extent of the responses did not differ significantly among the trials.

**Side effects.** There was no significant difference in the frequency of dry mouth. Blurred vision was somewhat more frequent after Atropen (13 subjects) than after intravenous (seven subjects) or intramuscular (nine subjects) atropine sulfate. Pain at the intramuscular injection site did not trouble the subjects after any of the injections and Atropen did not cause increased discomfort during injection.

## Discussion

**Atropine induced cardioacceleration.** The most striking differences among the various methods employed in this study to administer intramuscular atropine relate to the time course of the increase in heart rate. We found that Atropen produced a significantly earlier effect compared with conventional administration of either atropine sulfate or atropine citrate.



Fig 5 Radiograph showing the dispersion of radiopaque material in an anesthetized 17½ pound Newfoundland dog. The discrete globules on the right are the result of five injections with a conventional syringe. The more widely dispersed patches resulted from injections with Atropen.

Both mechanical and biochemical factors appear to contribute to the faster action of Atropen. It is a spring loaded device whose contents are injected more rapidly and under greater pressure than can be achieved with a conventional syringe. This results in a wider tissue dispersion immediately after injection (Fig 5).

The biochemical basis for the observation that atropine in citrate buffer (pH 4.3) acts more rapidly than unbuffered atropine sulfate is not known. The extent of dissociation of the two compounds immediately after injection may be a factor. Buffered atropine citrate complex may be more stable after injection than atropine sulfate and dissociate to a lesser extent. The undissociated form of a salt is uncharged and uncharged molecules penetrate capillary lipid membranes more rapidly than do charged molecules. Consequently the atropine citrate complex would be expected to enter the bloodstream faster than the more dissociated charged atropine base in atropine sulfate.

**Atropine induced cardiodeceleration.** Sinus nodal slowing is a manifestation of the transient paradoxical parasympathomimetic effect which occurs soon after parenteral administration of atropine.<sup>22,23</sup> In our study cardiac slowing occurred in some patients after administration of

atropine intramuscularly regardless of the type of solution or method of injection. Kalser and McLain<sup>24</sup> have established that slowing of heart rate after parenteral atropine occurs only when plasma concentration of atropine is low, the heart rate then increases as serum concentration of the drug rises.<sup>24</sup> This supports experimental observations that slowing occurs after small intravenous doses of atropine (0.3 to 0.6 mg intravenously) after larger intravenous doses administered slowly, and after intramuscular injections (because of slow absorption into the bloodstream) but less frequently after rapid intravenous injection of larger doses.<sup>25,26</sup> The rarity of sinus slowing after intravenous atropine noted in our study may be related to the relatively large size of the dose (10 mg) or to the rapid rate of intravenous administration of the drug.

While the parasympathomimetic property of atropine has been well documented, its mechanism and significance remain unclear. This effect is widely attributed to a central mechanism from observations that cardiac slowing could be abolished by general anesthesia as well as by sectioning the vagus nerve and that cardiac slowing could be produced in turtles by direct perfusion of the brainstem with atropine. More recently, however, the central origin of this effect has been

questioned by demonstrations that homatropine methylbromide a quaternary ammonium compound that does not penetrate the blood brain barrier will also cause transient cardiac slowing<sup>9</sup>

**Blood pressure** In supine normal subjects atropine may elevate systolic and diastolic pressures<sup>1</sup> The rise in both pressures reported here is probably caused by peripheral vasoconstriction rather than by an increase in cardiac output which would produce a decrease in diastolic pressure and elevation of pulse pressure

**Cardiac toxicity** All subjects in this study maintained sinus rhythm following atropine administration However attention has been called to the occurrence of transient arrhythmias including AV dissociation after intravenous administration of atropine to subjects without myocardial arrhythmias<sup>20-22</sup> In one such study a relatively large intramuscular dose of 11.0 to 14.0 mg of atropine sulfate was necessary to produce AV dissociation in healthy volunteers<sup>20</sup> Reports have also appeared describing increased ventricular irritability following intravenous injection of atropine in such subjects<sup>23-25</sup> In each of these cases the ventricular beats occurred during the period of tachycardia produced by the drug To our knowledge no reports of ventricular irritability during the transient period of cardiac slowing have been published

**Use of atropine during myocardial ischemia or infarction** The administration of atropine in a self injection device reliably produces cardioacceleration in normal subjects The effect is more rapid than with conventional intramuscular methods but slower than by intravenous infusion The amount of heart rate increase is similar regardless of the method used in the dosage established in this study But normal subjects are obviously different from patients with acute myocardial infarction What will be the effect of such a drug in these patients?

Stuckey and associates<sup>6</sup> have evaluated 27 patients in a coronary unit 17 of whom had definite myocardial infarction In these patients Atropen raised the heart rate from an average rate of 51 beats/minute to 96 beats/minute in 30 minutes Significant bradycardia was not produced by the injection Increase in systolic pressure followed use of the drug In two cases increased chest pain developed In this group of patients Atropen was effective in producing cardioacceleration

It seems highly unlikely however that a study comparable to the one reported here could be conducted in acutely ill patients with coronary disease in order to establish the relative effects of atropine given by different methods Valuable as such data may be we will have to depend on information which can be obtained in the controlled setting of a group of healthy subjects It seems probable though not established that similar results would appear

Although Atropen has been established as an effective and we suggest more effective method of delivering atropine where intramuscular or self injection is needed the fundamental question about the clinical application of the drug remains unanswered Such a discussion is beyond the intent or scope of this study Our support for the use of the drug in a self injection device is based upon the following (1) the method is effective in relieving vagal tone and elevating heart rate (2) Atropen produces a more rapid response than do conventional intramuscular injection methods (3) some patients with acute myocardial infarction bradycardia and hypoperfusion benefit from administration of atropine (4) some of these patients may be successfully treated outside the hospital when a self injection device may be particularly useful

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## Study of serum digoxin status in digitoxicity by radioimmunoassay

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The margin of safety between therapeutic and toxic doses of digitalis is not well defined and digitoxicity remains a problem in clinical practice. Though the therapeutic range of serum digoxin has been worked out to be between 0.8 ng/ml and 2 ng/ml, there are overlaps and nearly two thirds of the digitalized patients attending the hospital may have their serum digoxin concentration outside the therapeutic range. Variation in bioavailability of the different brands of digoxin and wide variation in the patients' responses to drugs present further problems.

The various symptoms and rhythm disturbances encountered in digitalized patients may in fact be due to inherent cardiac pathology though erroneously attributed to digitoxicity.

Myocardial digoxin concentration has been found to bear a constant ratio to serum digoxin level in persons with normal renal functions.

Radioimmunoassay has proved to be a sensitive method for estimation of serum digoxin. The present study has been taken up to evaluate digoxin status by radioimmunoassay and to correlate serum digoxin level with clinical and electrocardiographic evidences of digitoxicity.

### Materials and methods

Forty seven patients (32 toxic, 15 nontoxic control) with congestive heart failure who were

on treatment with Lanoxin brand of digoxin with daily dosage of 0.25 mg to 0.75 mg were included in the study. The patients were all adults admitted to S.C.B. Medical College Hospital, Cuttack, during the period March 1977 to March 1978. Thirty two patients had clinical and electrocardiographic evidence of digitoxicity according to the criteria laid down by Smith and Haber. Fifteen patients who had obtained optimum therapeutic benefit from digoxin therapy without any toxic features constituted the non-toxic control group in the study. None of the patients had renal failure. Thirty six patients suffered from rheumatic heart disease, six from ischemic heart disease, two from hypertensive heart disease and one from each of three other categories—namely congenital pulmonary and arteriosclerotic heart disease. Arteriosclerotic heart disease was diagnosed by thickened peripheral arterial wall, fundoscopic findings, a rim of calcification in the aortic knuckle demonstrated radiologically and by the absence of electrocardiographic evidence of ischemia. All the patients were clinically assessed and investigated for routine hematological values, serum protein, electrolytes, serum creatinine, blood urea and serum calcium. Serum digoxin was estimated by radioimmunoassay (RIA) using Lanoxin test Gamma kit obtained from Wellcome Reagent Ltd, England. The assay was repeated after the patients recovered from toxic manifestations after the withdrawal of digoxin.

Blood was collected for RIA 6 hours after the last dose of digoxin and serum was separated and

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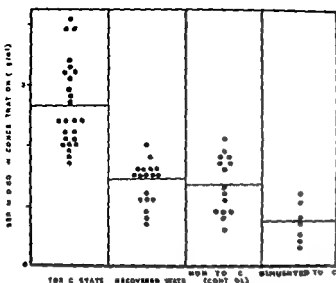


Fig 1 Scattergram showing serum digoxin concentration in Toxic Recovered Control and Simulated Toxic groups

preserved in deep refrigeration at  $-28^{\circ}\text{C}$  and was assayed using Lanoxi test Gamma kit with  $^{125}\text{I}$  digoxin. The result was plotted using count rates versus concentration of standards. This was used to determine the concentration of the digoxin sample obtained from patients. The data were statistically analyzed.

### Observation

All 47 patients (32 toxic 15 nontoxic control) were adults in an age group of 15 to 64 years. Toxicity was evenly distributed in all the age groups. Male to female ratio was 26:1. Out of 47 patients, 15 had relief of symptoms without any evidence of toxicity. Thirty-two patients were digitoxic. The clinical features of toxic patients included nausea, vomiting, anorexia, abdominal pain, lassitude and various arrhythmias (Table IA and Table IB). Seven patients out of these 32 cases were in fact in a state of underdigitalization as was subsequently revealed by RIA. These seven patients were designated as a simulated toxic but under digitalized (STUD) group.

The biochemical parameters such as serum protein, sodium, potassium, creatinine, calcium and blood urea are summarized in Table II.

The mean serum digoxin levels in toxic and nontoxic patients were  $2.64 \pm 0.68 \text{ ng/ml}$  and  $1.35 \pm 0.45 \text{ ng/ml}$  respectively. After recovery from the toxicity, the mean serum digoxin concentration dropped to  $1.43 \pm 0.2 \text{ ng/ml}$ . This was significantly lower than the level in toxic patients ( $P < 0.001$ ) and was similar to the

Table IA Clinical presentation of digitoxicity in 32 cases

Clinical presentation	No of cases	Per centage
Nausea	20	62.5
Anorexia	16	50
Vomiting	19	59.4
Epigastric pain	3	9.4
Excessive fatigue	1	3.1
Bradycardia	2	6.2
Irregular pulse (Pulsus bigeminus, multiple ectopics, AF and others)	32	100

patients in the nontoxic range (scattergram). The mean serum digoxin concentration in simulated toxic but under digitalized patients (STUD) was  $0.74 \pm 0.35 \text{ ng/ml}$ . This value when compared to that of nontoxic patients was significantly lower ( $P < 0.01$ ). The symptoms in patients of simulated digitoxicity (STUD) were in fact due to uncontrolled congestive heart failure which subsided with increasing dosage of digitalis (Table III).

Serum digoxin concentration was dose related. When dosage schedule and serum digoxin concentrations were analyzed in toxic and nontoxic patients, there was significant correlation ( $P < 0.001$ ) (Table IV).

All the patients had their serum creatinine and blood urea levels within the normal range (serum creatinine 0.7 to 2 mg per cent and blood urea 10 to 50 mg per cent). The value between 40 and 50 mg percent though in excess of normal has been taken as the upper limit of the normal range in our study in patients who showed no other clinical and laboratory evidences of renal dysfunction. Those with higher normal values of serum creatinine and blood urea had a higher serum digoxin concentration. Seven cases who had serum creatinine more than 1.5 mg/dl and blood urea more than 40 mg/dl had their serum digoxin concentration  $3.3 \pm 0.72 \text{ ng/ml}$ . In 18 toxic cases with serum creatinine less than 1.5 mg/dl and blood urea less than 40 mg/dl, the serum digoxin concentration was  $2.3 \pm 0.44 \text{ ng/dl}$  ( $P < 0.001$ ,  $T = 4.1$ ).

Digitoxicity was attained at a lower concentration in hypokalemic patients. Six toxic patients with serum potassium less than 3.5 mEq/l had serum digoxin concentration  $2 \pm 0.1 \text{ ng/ml}$ .

Table IB Electrocardiographic abnormalities in 14 cases of toxic patients

Category No	Rhythm	No of cases	Percentage
1	1 HB	4	17.5
2	1 HB with supraventricular ectopic	1	3.1
3	Ventricular bigeminy	3	9.4
4	1 HB with ventricular bigeminy	4	17.5
5	1 HB with ventricular trigeminy	1	3.1
6	Multiple ventricular ectopic	2	6.2
7	Multiple focal ventricular ectopic	3	9.4
8	PAT with varying degree of HB	2	6.2
9	AF with multifocal ventricular ectopic	1	3.1
10	Sinus tachycardia	1	3.1
11	Sinus bradycardia	2	6.2
12	Mobitz type II HB	1	3.1
13	Junctional escape rhythm	1	3.1
14	AF	6	18.8

Abbreviations: HB = heart block; PAT = paroxysmal atrial tachycardia; AF = atrial fibrillation

Table II Mean concentration of biochemical parameters in 47 cases

	Nontoxic	STUD group — cases	Toxic—25 cases
Serum protein (gm/dl)	6.2 ± 0.4	6.0 ± 0.33	6.1 ± 0.44
Serum Na (mEq/L)	139.3 ± 2.5	140 ± 4.8	137.9 ± 4.1
Serum K (mEq/L)	4.2 ± 0.6	4.14 ± 0.19	3.8 ± 0.57
Serum creatinine (mg/dl)	0.75 ± 0.9	0.75 ± 0.2	0.9 ± 0.49
Blood urea (mg/dl)	30.1 ± 10.4	32.1 ± 10.9	46.5 ± 12.1
Serum calcium (mg/dl)	10.3 ± 0.5	10.3 ± 0.37	10.2 ± 0.6

STUD = simulated toxic undigoxinized group

Table III Serum digoxin concentration in simulated toxic group (STUD) before and after increase in dosage of digoxin in 4 cases

Case no	Before increasing the dose (ng/ml)	After increasing the dose (ng/ml)
17	0.4	1.6
20	0.3	1.2
21	0.5	1.8
22	0.7	1.7

In the other three cases repeat digoxin levels could not be done

Nineteen toxic patients with serum potassium value more than 3.5 mEq/L had the mean digoxin concentration  $2.83 \pm 0.97$  ng/ml ( $P < 0.05$ )

No significant correlation could be established between serum digoxin and serum sodium and calcium

Routine estimation of hematological values and serum protein carried out in these patients revealed a low average nutritional status

Table IV Mean serum digoxin concentration in relation to different dosage schedule

	Serum digoxin level in ng/ml		t	p
	Nontoxic	Toxic		
Dosage—0.25 to 0.5 mg/dav				
No of cases	7	10		
Mean ± SD	0.91 ± 0.18	2.06 ± 0.28	9.58	0.001
Dosage—0.5 to 0.75 mg/dav				
No of cases	8	15		
Mean ± SD	1.4 ± 0.22	3.03 ± 0.59	6.19	0.001

## Discussion

Estimation of serum digoxin before during and after recovery from digitoxicity showed that serum digoxin concentration was highest during toxicity. Serum concentration higher than therapeutic range is necessary to produce digitoxicity. There was no correlation of arrhythmia with mean serum digoxin concentration contrary to

Table V Serum digoxin concentrations in various studies (nontoxic and toxic patients) in ng/ml

Authors	Method	Mean concentration		Statistical significance
		Nontoxic	Toxic	
Smith Butler and Haber <sup>1</sup> (1969)	RIA	13	33	Yes
Grahame Smith and Everest (1969)	86 Rb uptake	24	57	Yes
Smith & Haber <sup>2</sup> (1970)	RIA	14	37	Yes
Chamberlain et al (1970)	RIA	14	31	Yes
Oliver Parker and Parker (1971)	RIA	16	30	Yes
Hoeschen and Proveda (1971)	RIA	08 13	28	Yes
Fogelman et al. (1971)	RIA	14	17	No
Evered and Chapman (1971)	RIA	138	336	Yes
Beller et al (1971)	RIA	10	23	Yes
Bertler and Redfors (1971)	86 Rb uptake	0.9	2.4	Yes
Butler (1972)	RIA	15	28	Not stated
Whiting et al (1973)	RIA	08	32	Yes
Carruthers et al. (1974)	RIA	14	276	Yes
Singh et al. (1975)	RIA	23	39	Not stated
Calesnick & Dinah (1976)	RIA	184	34	Yes
Present study (1978)	RIA	13 ± 0.45	26 ± 0.68	Yes (p < 0.001 t = 6.8)

the observations of Smith and Haber.<sup>3</sup> They observed significantly higher levels of serum digoxin in supraventricular tachycardia with block than in atrial fibrillation.

In the present series seven patients diagnosed to be toxic on clinical and electrocardiographic grounds were actually nontoxic. Their serum concentration was low and they improved with a higher dosage of digitalis. This observation emphasizes the value of correlating the clinical picture with serum digoxin concentration for distinguishing the real from the simulated digoxin toxic state.

There was some overlap in serum digoxin levels among toxic and nontoxic groups. The range of serum digoxin in the nontoxic group was 0.5 ng/ml to 1.8 ng/ml and in the toxic group it was 1.6 ng/ml to 4.1 ng/ml. Only two patients in the toxic group had a serum level below 1.8 ng/ml. Ten out of 25 toxic cases had serum concentration more than a mean concentration of 2.6 ng/ml.

The mean serum concentration in digoxin toxicity in the present series has been compared with the findings of other workers.<sup>4</sup> (Table V) Singh and associates<sup>5</sup> have found a mean toxic level at 3.9 ng/ml. The low average nutritional status and body weight may explain the lower mean values in our patients.

Renal impairment hastens the process of digoxin

toxicity by retarding the excretion of digoxin. In this study serum creatinine, blood urea, and serum digoxin are positively correlated. The greater the value of serum creatinine and blood urea, the higher was the serum digoxin concentration in digoxin toxicity. This finding is in accord with the observations of Beller and colleagues.<sup>6</sup>

Digoxin toxicity in the present study has occurred at a lower serum concentration in hypokalemic patients. Hypokalemia renders the patients more sensitive to digoxin and narrows down the margin of safety so that even in therapeutic concentrations of digoxin, toxic symptoms become manifest. There is a positive correlation between the serum digoxin level and serum potassium. The lower the serum potassium, the lower the serum digoxin level at which toxicity develops.

The serum digoxin concentration in the present study has been found to be dose related (Table IV). This observation is consistent with the findings of Carruthers and co-workers<sup>7</sup> and of Beller and associates.<sup>8</sup>

Four cases of ischemic heart disease showed toxic features at a lower concentration (1.7 ng/ml to 3 ng/ml) which may be due to increased sensitivity of the damaged myocardium. This observation supports the findings of earlier workers.<sup>9</sup> The present study shows that undernutrition, hypokalemic status, and cardiac decompensation due to ischemic heart disease are the

conditions in which the margin of safety between the therapeutic and toxic range of serum digoxin concentration is narrowed down so that toxicity ensues at a lower dose level. Higher normal values of serum creatinine and blood urea even in the absence of renal failure are associated with a hyperdigoxinemic state and digtoxicity. This situation is often encountered in digitalized patients who are on diuretics and restricted fluid intake.

To conclude there is a great variability between the serum concentration of digoxin and toxic manifestations. When both clinical and electrocardiographic findings are correlated with serum digoxin concentration giving due weight to etiopathology of the cardiac condition the therapeutic dose range can be distinguished from the toxic and under digitalized state.

Serum digoxin estimation by RIA serves as a useful procedure not merely for detection of digtoxicity but for ensuring optimal therapeutic response and for forestalling toxic effect by appropriate adjustment of dosage.

### Summary

Forty seven patients who were being treated with digoxin in a daily dose range of 0.25 mg to 0.75 mg were the study material. Thirty two patients were toxic. Seven patients out of these 32 were in an under digitalized state and 15 patients were nontoxic. All patients were clinically assessed and investigated for routine hematological value serum protein electrolytes serum creatinine blood urea and serum calcium.

Serum digoxin concentration was estimated in all cases by the radioimmunoassay method. The assay was repeated after the patients recovered from toxic manifestations on withdrawal of the digoxin. The mean serum digoxin level in toxic patients ( $2.64 \pm 0.68$  ng/ml) was significantly higher ( $P < 0.001$ ) than that in nontoxic patients ( $1.35 \pm 0.45$  ng/ml). After recovery from toxicity the mean serum digoxin level ( $1.43 \pm 0.32$  ng/ml) was found to be significantly lower than the level in the toxic patients and was similar to the level in patients of the nontoxic group. Seven patients whose symptoms simulated digtoxicity were in fact in an under digitalized state

( $0.74 \pm 0.35$  ng/ml) and their symptoms were relieved with a higher dosage of digoxin. In this study an attempt has been made to show the importance of the estimation of serum digoxin in the assessment of therapeutic and toxic effects of the drug so as to modify the dosage schedule for the optimal therapeutic response.

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# Electrocardiographic changes in cerebrovascular hemorrhage

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Patients with central nervous system disorders often have abnormal electrocardiograms in the absence of known organic heart disease Burch Myers and Abildskov were the first to report electrocardiographic abnormalities in patients with cerebrovascular accidents Since then many reports have appeared in the literature<sup>1-4</sup> This study was done utilizing information obtained by computerized tomography (CT scan) to verify and localize the site of the hemorrhage for purposes of correlation of the hemorrhagic event with the abnormalities noted on the electrocardiogram

## Materials and methods

A total of 186 patients records representing all cases with cerebral hemorrhage documented by CT scan at the University of Louisville Affiliated Hospitals from July 1977 to March 1979 were reviewed All patients were scanned on the EMI CT 1010 dedicated brain scanner in the University Hospital Most patients were examined on an emergency basis because of rapid neurological deterioration and received an unenhanced scan only Those patients who were enhanced received

60 ml of Renografin 60 followed by 300 cc of Reno MD IP All patients with evidence of any preexisting heart disease were excluded Particular care was focused on eliminating any patient from the study with evidence of atherosclerotic heart disease including angina pectoris or myocardial infarction those with ischemic changes during resting or exercise electrocardiograms and those with hypertension congenital valvular, or cardiomyopathic heart disease Patients under treatment with any cardiac drugs were excluded Only patients whose earlier electrocardiograms were normal were included for the study Electrolyte profiles were a requisite for inclusion The following report is of 60 such patients Criteria for electrocardiographic diagnosis were those reported summarized by Cooksey and colleagues<sup>5</sup>

This is a report then, of 60 patients with cerebrovascular hemorrhage who had no evidence of prior cardiac abnormalities drug or reasons for electrolyte effect abnormalities on their electrocardiogram

## Results

The regions of CT scan abnormality were grouped as deep cerebral superficial cerebral and posterior fossa The groups were further divided by etiology The superficial cerebral group was subgrouped into traumatic and spontaneous divisions No history of prior trauma was present in either the deep cerebral or posterior fossa groups Age and sex of each group are also shown (Table I)

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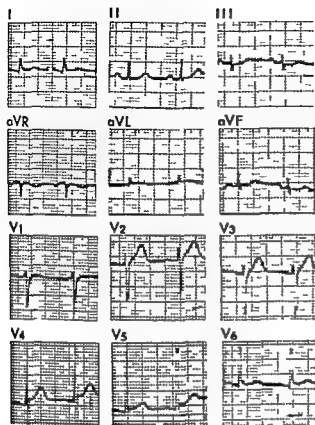


Fig 1A ECG obtained two years (February 15 1979) prior to the present illness is normal.

Table 1 Regions of hemorrhage with numbers of patients by age and sex

	Number of patients	Mean age (range)	Sex	
			Male	Female
Deep cerebral				
A Basal ganglia	8	67 (50-89)	5	3
B Thalamus	5	60 (53-66)	2	3
Superficial cerebral traumatic				
A Frontal	6	32 (16-69)	6	0
B Temporal parietal	10	27 (21-48)	9	1
C Occipital	0			
Nontraumatic				
A Frontal	5	52 (34-68)	3	3
B Temporal parietal	20	63 (14-85)	10	10
C Occipital	2	(55-83)	1	1
Posterior fossa				
A Brain stem	8	53 (20-63)	7	1
B Cerebellar hemisphere	1	56	0	1

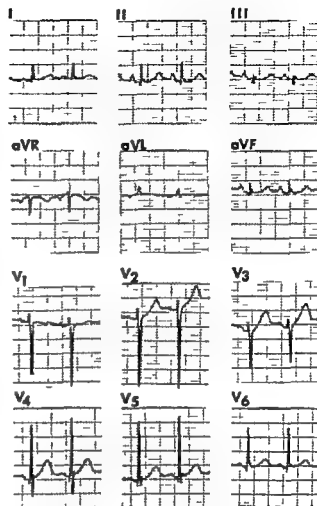


Fig 1B ECG obtained shortly after admission (February 13 1979) shows a sinus tachycardia of about 120 beats per minute

Sinus tachycardia was commonly seen occurring in all categories but was never seen in the majority of patients in any group (Table II)

Sinus bradycardia was less commonly seen and occurred with traumatic frontal lobe hemorrhage (33%) and nontraumatic temporal parietal hemorrhage (10%)

Sinus arrhythmia occurred in 33% of patients with traumatic frontal lobe lesions

The sudden onset of atrial fibrillation seemed only associated with hemorrhage into the brain stem area (25%). The ventricular response rate was always rapid ranging from 130 to 180

Supraventricular tachycardia occurred in 33% of the group with traumatic frontal lobe hemorrhage

Atrioventricular block of first degree occurred



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PICa	LAFB	LAE	LVE	ASSTT	QT	Neurogenic T	IMI	Uptakes	PE
10	10	20	17	31 20 50	1	20	10	15	32
100									

and one with near reversion to baseline (February 22 1979) (Figs 1 A B, C and D) CT scan (Fig 2) performed the day of admission showed increased uptake overlying the pituitary secondary to aneurysmal rupture of the anterior communicating artery confirmed by cerebral arteriography.

### Discussion

Abnormal electrocardiograms occurring with acute cerebrovascular events have been previously described.<sup>2-14</sup> The incidence of ECG changes in a group of subarachnoid hemorrhages was 71.5% described by Kreis and associates. In groups with intracerebral hemorrhage and unclassified cerebrovascular accidents the figures of 67.1% and 41.1% have been reported. In this group 80% (62 patients) had some change from their earlier electrocardiogram.

What then are the possible causal relationships that could explain the presence of electrocardiographic abnormalities in patients suffering from a variety of acute intracranial disease?

Kaye McDonald and Randall have demonstrated that subendocardial hemorrhages are an uncommon finding after prolonged and intense sympathetic activity on the heart. Such a condition of intense sympathetic drive is to be expected during the terminal stages of acute intracranial hemorrhages. However actual myocardial damage that can be detected pathologically is unusual and the vast majority of cases brought to autopsy have revealed a normal heart.

Direct stimulation of various areas of the brain is known to result in abnormal electrical patterns of the heart. Stimulation of the frontal lobe, the orbital cortex, the anterior part of the temporal lobe, the insula, and the angular gyrus commonly produces alterations in ST segment duration and amplitude as well as changes in the T wave duration. Areas where stimulation is associated with ventricular ectopy and aberration of ventricular conduction are primarily found in the limbic lobe, the hypothalamus and the central gray matter. Cropp and Manning<sup>3</sup> have suggested that lesions of area 13 on the orbital surface of the frontal lobe may be responsible for the ECG changes. Poole has written on the induction of arrhythmias and ST segment and T wave changes in the ECG during manipulation of the circle of Willis in man.

A variety of abnormalities of depolarization and cardiac automaticity are seen with stimulation of both cortical and subcortical areas.

Stimulation of the stellate ganglia produces consistent abnormalities of repolarization of the ventricular myocardium. In the work in dogs by Yanowitz and associates, right stellate ganglionectomy with intact left stellate or left stellate stimulation resulted in T waves of increased area and prolonged QT intervals in 45 of 45 dogs.

Left stellate ganglionectomy with an intact right stellate or stimulation of the right stellate ganglion produced a significant T wave inversion less often in 14 of 35 dogs. Removal of the

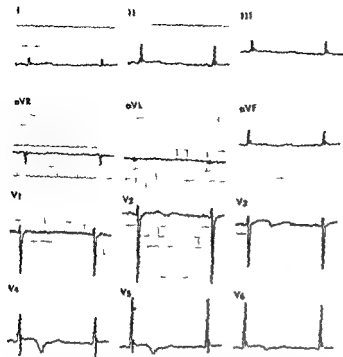


Fig 1C ECG obtained on February 19 1979 show repolarization abnormalities which began shortly after the ECG taken on February 13 and which were maximal on February 19 Sinus bradycardia at about 40 beats per minute was also present

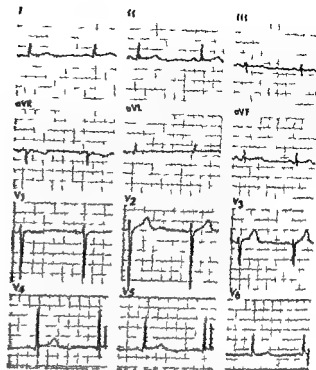


Fig 1D Three days following (February 22 1979) the previous tracing except for sinus bradycardia with associated Q waves the electrocardiogram has returned essentially normal

ganglion also produced abnormalities. Removal of the right ganglion resulted in refractory period prolongation on the anterior surface of the left ventricle. Left stellate ganglionectomy produced refractory period prolongation on the posterior surface of the left ventricle.

The vagus nerve influences the heart's sinus node by phase-related pulses of discharge.

If repetitive bursts of vagal impulses arrive at certain phases of the cardiac cycle, the sinus node will become very unstable and a severe sinus arrhythmia will occur. At other phases of the cardiac cycle, vagal stimulation serves to stabilize the sinus node. In this instance, the slow rate of discharge results in a marked but regular bradycardia.

In addition to the vagal influence, some ECG changes are mediated through the sympathetic pathway. Porter and associates were able in rats to produce T wave inversion by stimulation in the central hippocampus. The T wave inversion could be blocked by transection of the cervical spinal cord interrupting sympathetic fibers. In humans, a strong cortical connection exists between the hypothalamus and the orbitofrontal cerebral

cortex by way of the fronto-hypothalamic pathway which allows hypothalamic efferents to reach the various autonomic tegmental nuclei whose cell bodies connect to the sympathetic cell bodies in the thoraco-lumbar gray matter. A complete pathway for sympathetic outflow then exists from the cerebral cortex, especially the orbitofrontal area to the heart via the stellate ganglia.

In this retrospective study of 65 patients, there seemed to be a high incidence of electrocardiographic abnormalities in frontal lobe hemorrhage, both spontaneous and traumatic, compared to hemorrhages in other areas. Neurogenic T waves were frequently seen only in frontal lobe lesions (50%). The sudden onset of atrial fibrillation in association with brain stem hemorrhages was noted in 25% of the cases.

We conclude that neurologically induced ECG abnormalities are frequent in anterior cerebral events. Further, the sudden development of electrocardiographic abnormalities in the setting of anterior cerebral or brain stem hemorrhage suggests consideration of a cerebral association rather than a primary myocardial event.

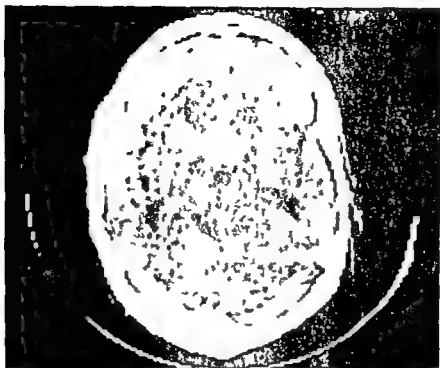


Fig 2 CT scan shows a focal hemorrhage between the two frontal lobes anterior to the third ventricle secondary to a subsequently documented anterior communicating artery aneurysm (arrow)

## Summary

The electrocardiographic abnormalities found in localized cerebrovascular hemorrhage which have been documented by computerized tomography (CT) scans are described. Frontal lobe hemorrhages are associated especially with the electrocardiographic abnormalities of QT prolongation and neurogenic T waves. Brain stem hemorrhage seems to be associated with noncardiogenic pulmonary edema and sudden development of atrial fibrillation. It is proposed that the cause of ECG abnormalities in association with lesions in the vicinity of area 13 on the orbital surface of the frontal lobe or around the circle of Willis results from alterations in sympathetic and parasympathetic tone mediated by fibers from the orbital frontal area to the heart via the stellate ganglia.

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## The pediatric spectrum of dynamic left ventricular obstruction

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The original descriptions of hypertrophic subaortic stenosis (IHSS) have been associated with echocardiographic features of asymmetric hypertrophy of the interventricular septum (ASH) abnormal systolic anterior motion of the mitral valve (SAM) and midsystolic aortic valve closure.<sup>1</sup> A unified concept of IHSS as an autoimmune dominant disease characterized by ASH and disorganized myocardial histology has been proposed.<sup>2</sup> When subaortic obstruction was present both SAM and midsystolic aortic closure were frequently found.<sup>3</sup>

Recently the specificity of ASH and SAM as indicators of IHSS has been challenged. ASH has been demonstrated in many types of congenital heart disease.<sup>4</sup> SAM without ASH has been found in patients with and without concentric myocardial hypertrophy who have associated intraventricular pressure gradients. Several patients with SAM have been found to have a mid ventricular pressure gradient or left ventricular cavity obliteration rather than subaortic obstruction. Both SAM and midsystolic closure of the pulmonic valve have been associated with dynamic left ventricular outflow obstruction in patients with D transposition of the great arteries.<sup>5</sup>

Echocardiographic and hemodynamic features similar to that seen in adults with IHSS have been reported in association with systemic hyper-

tension aortic stenosis coarctation of the aorta and a variety of other congenital heart diseases. Most reports have concentrated on an adult population. This study evaluated a population of pediatric patients over a four year period to evaluate the diverse clinical presentations echocardiographic findings and hemodynamic data that are associated with dynamic left ventricular outflow obstruction. Furthermore an attempt was made to identify the pathophysiologic mechanisms that might lead to this obstruction.

### Patients and methods

The study group comprised 21 pediatric patients with classic echocardiographic signs of subaortic obstruction (or subpulmonic in patients with D TGA) and/or cardiac catheterization documented dynamic left ventricular obstruction at our institution from 1975 through 1978. The patients were divided into three groups based on their age at presentation. Nine patients were evaluated during the first month of life and were designated *Group A* (neonates). Six patients presented between four months and two years of age and were called *Group B* (infants). The remaining six patients were eight to 17 years of age and were designated *Group C* (children and adolescents) (Table I).

Among the *Group A* patients four were infants of diabetic mothers, two had idiopathic hypertension, one had hypertension from coarctation of the aorta, one had tetralogy of Fallot and the remaining neonate had idiopathic hypertrophic cardiomyopathy. The diagnoses in the six *Group B* patients were coarctation of the aorta (1), D transposition of the great arteries (4) and

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Table I Echocardiographic and catheterization data on the 21 pediatric patients comprising the study population

Pat tent no	Diag noses	Age	Treat ment	Echo data						Catheterization data					
				IVS	LVW	IVS	RVW	SAM	MSC	R/P	LVP	R PSG	L PSG		
													Basal	Provoked	
1	IDM	1 d	None	12	06	20	04	+	+	ND	ND	ND	ND	ND	
		25 d	None	07	04	175	04	+	—	ND	ND	ND	ND	ND	
2†	IDM	1 d	Digoxin	14	06	233*	06	+	+	ND	ND	ND	ND	ND	
3	IDM	1 d	None	09	03	30	06	+	—	ND	ND	ND	ND	ND	
4	IDM	2 d	None	11	05	22	02	+	+	ND	ND	ND	ND	ND	
		33 d	None	06	03	20	02	—	—	ND	ND	ND	ND	ND	
5	HT	3 d	Digoxin	03	03	10	03	—	—	ND	ND	ND	ND	ND	
		3 wk	Prop	05	03	167	04	—	—	110	110	0	20	40	
6†	Idio	4 d	Digoxin	07	05	129	04	+	+	55	100	0	20	ND	
		3 wk	Prop	07	04	140	03	+	+	ND	ND	ND	ND	ND	
7	CoA	3 wk	None	09	06	150	03	+	+	40	170	15	ND	ND	
		18 m	Digoxin	06	05	120	02	—	—	ND	ND	ND	ND	ND	
8	HT	3 wk	Prop	08	07	114	07	+	+	50	100	0	0	95	
	NT	6 m	Prop	04	04	100	03	—	—	ND	ND	ND	ND	ND	
9	TOF	1 m	None	04	03	133	05	+	+	80	90	NA	0	ND	
		1 yr	None	05	06	084	06	+	+	100	100	NA	0	ND	
10	CoA	7 m	None	09	07	129	04	+	+	100	200	45	60	ND	
11	IHSS	2 y	None	ND	ND	ND	ND	ND	ND	90	900	65	100	ND	
	S/P myec	7 y	Prop	18	15	120	04	+	+	44	180	14	60	ND	
12	D TGA	5 m	S/P BAS	04	03	133	05	+	+	100	60	0	30	ND	
13	D TGA	5 m	S/P BAS	03	04	075	05	+	+	90	40	0	20	ND	
14	D TGA	5 m	S/P BAS	05	04	120	05	+	+	85	60	0	25	ND	
15	D TGA	5 m	S/P BAS	04	03	133	05	—	+	110	65	0	35	ND	
16	IHSS	8 y	None	ND	ND	ND	ND	ND	ND	30	230	0	130	ND	
	S/P myec	14 y	Prop	15	09	167	04	+	+	30	120	0	20	90	
17	Conc	10 y	Prop	12	15	080	03	+	+	30	130	0	0	110	
	Conc	12 y	None	08	08	100	03	—	—	ND	ND	ND	ND	ND	
		13 y	None	12	11	109	03	—	—	28	130	0	0	190	
		14 y	Prop	11	11	100	04	—	—	ND	ND	ND	ND	ND	
19	IHSS	13 y	None	ND	ND	ND	ND	ND	ND	24	136	0	40	190	
	S/P myec	18 y	Prop	20	16	125	04	+	+	37	180	0	60	ND	
20	IHSS	16 y	None	ND	ND	ND	ND	ND	ND	53	145	20	20	100	
		20 y	Prop	20	11	182	03	+	+	85	190	60	60	130	
21	IHSS	17 y	None	16	08	200	03	+	—	ND	ND	ND	ND	ND	

Abbreviations and symbols: ASH = asymmetric septal hypertrophy; BAS = balloon atrial septostomy; CoA = coarctation of the aorta; Conc = concentric left ventricular hypertrophy; d = age in days; D TGA = D transposition of the great arteries; HT = systemic hypertension; Idio = idiopathic; IDM = infant of a diabetic mother; IHSS = idiopathic hypertrophic subaortic stenosis; IVS = interventricular septum; L PSG = peak systolic pressure gradient left side; LVP = peak left ventricular systolic pressure; LVW = left ventricular posterior wall; m = age in months; MSC = mitral aortic closure; myec = myectomy; NA = does not apply; ND = not done; NT = normotension; Prop = propranolol; R PSG = peak systolic pressure gradient right side; RV/P = peak right ventricular systolic pressure; RVW = right ventricular anterior wall; SAM = aortic aortic stenosis of the mitral valve; S/P = status-post; TOF = tetralogy of Fallot; wk = age in weeks; yr = age in years; + = present; — = absent.

†Patient died.

IHSS (1) Among the Group C patients four had IHSS and two had concentric left ventricular hypertrophy. None of the Group C patients had hypertension, coarctation of the aorta, or aortic stenosis.

All patients had echocardiographic examinations which were performed with commercially available ultrasound transducers, ultrasono-

scopes and strip chart recorders. Measurements of the right ventricular anterior wall (RVW), interventricular septum (IVS) and left ventricular posterior wall (LVPW) were made at the onset of the electrocardiographic QRS complex in the plane of the tips of the mitral valve leaflets in older patients and in the plane of the posterior mitral valve leaflet in infants and neonates (Fei-

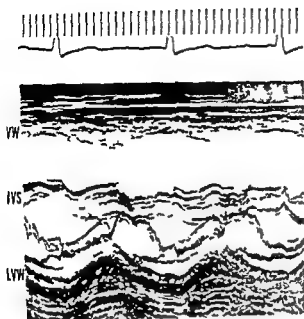


Fig 1 This echocardiogram is from a patient with D transposition of the great arteries and demonstrates systolic anterior motion of the mitral valve (patient No 14) IVS = interventricular septum LVW = left ventricular posterior wall RVW = right ventricular anterior wall

genbaum's transducer positions 1 and 2 respectively). Care was taken to visualize the right side of the IVS as this may be confused with the tricuspid valve annulus. Two independent observers measured the echocardiograms to the nearest 1.0 mm and the values for each measurement are the average of those determinations.

Measurements greater than normal as defined by Rogé and associates study<sup>1</sup> were considered abnormal and an IVS/LVPW ratio equal to or greater than 1.5 was considered to indicate asymmetric septal hypertrophy. Systolic anterior motion of the mitral valve was diagnosed after recording the mitral valve below the level of the mitral annulus and observing rapid anterior motion and return. Both aortic valve leaflets (pulmonic leaflets in patients with D transposition) were visualized in order to observe mid systolic closure.

Most patients underwent cardiac catheterization. The exceptions were four infants of diabetic mothers (IDMs) and one asymptomatic adolescent with IHSS. Infants less than two months of age received no premedication while older patients received either diphenhydramine hydrochloride (1 mgm/kg) and droperidol (0.1 mgm/kg) or meperidine hydrochloride (1 mgm/kg) and hydroxyzine hydrochloride (1 mgm/kg). Further

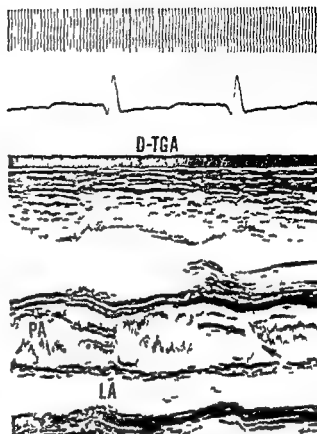


Fig 2 This echocardiogram is also from patient No 14 and shows the systolic flutter and mid systolic closure (denoted by the arrow) which implies subpulmonic obstruction. This infant had a subpulmonic gradient of 20 mm Hg. D-TGA = D transposition of the great arteries LA = left atrium PA = pulmonary artery

sedation or anesthesia was achieved when necessary with intravenous ketamine hydrochloride (1 mgm/kg), diazepam (0.1 mgm/kg) or diphenhydramine hydrochloride (1.0 mgm/kg). Standard right and left heart catheterizations were performed and all pressures were recorded prior to angiography. The left ventricular pressures were recorded with a multiple hole catheter in an attempt to prevent spurious elevation of pressures by catheter entrapment. When the left ventricle was approached through the aortic valve a pigtail catheter (Cook Inc) was used.

An attempt was usually made to provoke or to amplify a left ventricular aortic pressure gradient with post-ectopic beats, isoproterenol infusion or supine exercise. Propranolol was sometimes given in an attempt to lessen the left ventricular aortic gradient. Angiographic assessment of the right and left ventricles was performed in all patients who underwent cardiac catheterization. If isopro-



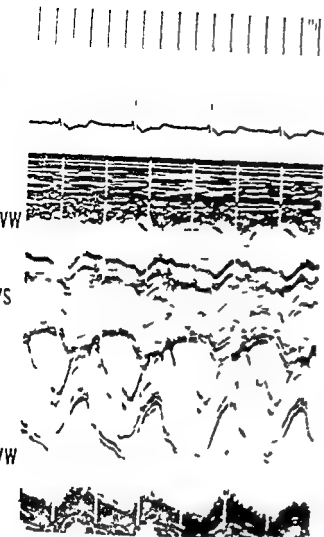


Fig 3 The echocardiogram is from patient No 19 and shows a marked increase in thickness of the interventricular septum and posterior left ventricular wall. The patient had a family history of IHSS and had undergone a myectomy several years before this examination. IVS = interventricular septum, LVW = left ventricular posterior wall, RVW = right ventricular anterior wall.

propranolol had been used then at least 20 minutes elapsed between the cessation of isoproterenol and performance of angiography so that the heart rate could return to the basal level.

**Results**  
**Medical**  
**Group A—Neonates** Among the nine neonates in this study eight presented with mild to severe congestive heart failure. Four patients were treated with digoxin prior to establishing a definite diagnosis and two of these died, one despite continuation of the digoxin and the administration of propranolol. The seven surviving neonates improved with propranolol alone, digoxin (1), or no medical therapy (4). The patient with

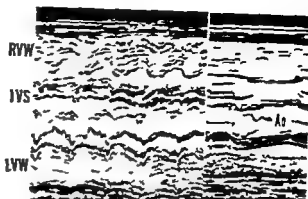


Fig 4 This composite echocardiogram is from patient No 8 who was a hypertensive neonate. There is severe hypertrophy of the right ventricular wall, interventricular septum, and left ventricular wall. In addition there is systolic anterior motion of the mitral valve and mid systolic closure of the aortic valve. These abnormalities all resolved by six months of age when the patient was receiving propranolol. Ao = aorta, IVS = interventricular septum, LVW = left ventricular posterior wall, RVW = right ventricular anterior wall.

tetralogy of Fallot became increasingly cyanotic and had a Blalock-Tausig shunt at one year of age.

**Group B—Infants** Six infants presented for evaluation of a cardiac murmur (patients No 10 and 11) or for increasing cyanosis (patients No 12 to 15). None had congestive heart failure. The infants with D transposition all underwent a successful Mustard procedure while the infant with IHSS underwent a myectomy. All patients are currently well.

**Group C—Children and Adolescent** Six children in this group presented for evaluation of a cardiac murmur and were either asymptomatic or had mild exercise intolerance. Two were treated with both surgery and propranolol, three with propranolol alone, and one received no treatment.

#### Echo data (Table I)

**Group A** The LVPW thickness was increased in four of nine patients. The IVS was thicker than normal in eight of nine neonates with an elevated IVS/LVW ratio in six patients. The RVW thickness was increased in four patients. Seven patients had SAM and six of these seven had mid-systolic closure of the aortic valve.

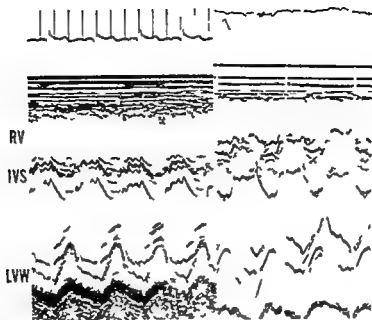


Fig 5 These echocardiograms are from patient No 11 and demonstrate the development of concentric left ventricular hypertrophy over a two year period IVS = interventricular septum LVPW = left ventricular posterior wall RV = right ventricle

**Group B** The LVPW and IVS were each increased in two infants the IVS/LVPW ratio was elevated in only one patient. The RVW was thick in the four infants with D transposition. All patients showed mid systolic closure and five demonstrated SAM (Figs 1 and 2).

**Group C** The LVPW was increased in four patients while all patients demonstrated a thick IVS (Fig 3). The IVS/LVPW ratio was elevated in four cases. The RVW was normal in all patients. There was SAM in five patients with accompanying mid systolic closure in four of these cases.

**Sequential echo data** Sequential echocardiograms were available from seven neonates (Group A). Five survivors demonstrated resolution of hypertrophy and signs of subaortic obstruction. The most striking example (patient No 8) had a normal echocardiogram by six months of age (Fig 4). Two older infants (Group B) had sequential echocardiograms which continued to show SAM and midsystolic closure. Sequential studies were available from one child in Group C whose concentric left ventricular hypertrophy progressed over a two year period (Fig 5).

#### Catheterization data

**Group A** Four patients in this group who underwent cardiac catheterization had a left ventricle aortic pressure gradient at rest or with provocation which ranged from 20 to 40 mm Hg.

This gradient could be ablated with propranolol in patient No 5 (Fig 6). Three neonates had a right ventricle pulmonary artery gradient in one case this was attributable to tetralogy of Fallot. Angiography demonstrated myocardial hypertrophy and deformity of the left and right ventricular cavities with encroachment of the right ventricular outflow tract in two cases (no 5 and 7) with a right ventricular pulmonary artery gradient.

**Group B** Two of the infants in Group B had a left ventricle to aorta gradient of 60 mm Hg while the remaining four infants with D transposition had subpulmonic gradients ranging from 25 to 35 mm Hg. The angiograms from patients No 10 and 11 showed myocardial hypertrophy with deformity of the left and right ventricular cavities. Infant No 10 showed left ventricular cavity obliteration during systole. The four infants with D transposition each had a large right ventricle with a small left ventricle and narrowing of the subpulmonic region during ventricular systole.

**Group C** Five of the six patients in this category had cardiac catheterization studies and all of these had left ventricle aorta pressure gradients at rest or with provocation. Two patients with concentric hypertrophy (No 17 and 18) had no gradient at rest but developed large gradients (110 and 120 mm Hg) during isoproterenol infusions (Fig 7). Only one patient in Group C had a right

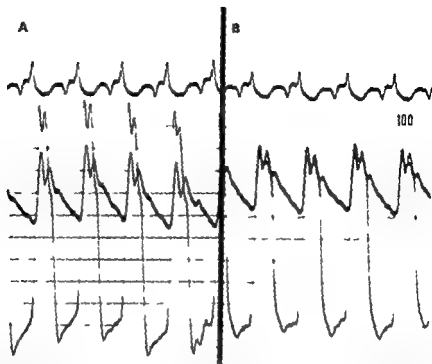


Fig 6 These pressure tracings were obtained before (panel A) and after (panel B) the administration of intravenous propranolol to patient No. 1. The left ventricle and aortic pressure curves are displayed and the pressure gradient of 20 mm Hg (left panel) was ablated with propranolol (right panel). Each horizontal line represents 10 mm Hg.

ventricle pulmonary artery pressure gradient Angiography showed typical features of IHSS in three patients and systolic left ventricular cavity obliteration in the two cases with concentric LV hypertrophy (Fig 8).

### Discussion

Many different anatomic and physiologic cardiac states may result in echocardiographic and hemodynamic findings that are similar to IHSS. The spectrum of dynamic left ventricular obstruction in children appears even broader than in adults because of the addition of neonatal abnormalities (e.g. infants of diabetic mothers) and congenital cardiac diseases. The two adolescents in this series with concentric left ventricular hypertrophy and cavity obliteration are younger than patients in other reports and represent the first documentation of this entity in the pediatric age group. Furthermore, the infant in this series with tetralogy of Fallot and signs of left ventricular obstruction is unique.

We believe the term hypertrophic obstructive cardiomyopathy is appropriate to describe a constellation of hemodynamic, echocardiographic and angiographic findings which occur with dynamic left ventricular obstruction. The most

common of these disorders is IHSS but other patients have hypertrophic cardiomyopathy that can be attributed to one or several predisposing factors. These factors include encroachment of the left ventricular cavity or its outflow tract, altered hemodynamics of left ventricular ejection, myocardial hypertrophy increased after load and genetic predisposition. Subaortic obstruction can be attributed to SAM of the mitral valve and to posterior bulging of the septum into the left ventricular outflow tract while myocardial hypertrophy may encroach on the left ventricular cavity. Altered ventricular ejection hemodynamics have been suggested as the primary event in hypertrophic cardiomyopathy.<sup>10</sup> The increased velocity of ejection through the left ventricular outflow tract may exacerbate the narrowing of this structure through the Venturi effect.<sup>11</sup> Myocardial hypertrophy either as a primary disorder or secondary to increased left ventricular overload contributes to the encroachment of the left ventricular cavity and to enhancement of its contractility. Finally, a genetic predisposition is strongly associated with the development of IHSS or with the occurrence of hypertrophic cardiomyopathy in rarer syndromes such as Noonan's syndrome, Pompe's

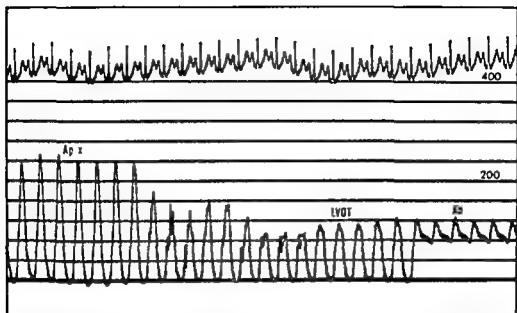


Fig 7 This pressure tracing is from patient No 18 who had concentric left ventricular hypertrophy. While there was no left ventricular aortic pressure gradient at rest, a gradient of 120 mm Hg could be induced with isoproterenol or with supine exercise. Each horizontal line represents 40 mm Hg. Ao = ascending aorta. Apex = left ventricular apex. LVOT = left ventricular outflow tract.

disease or Friedreich's ataxia<sup>3</sup>.

Among our patients several had familial IHSS or idiopathic concentric left ventricular hypertrophy while for other patients we could propose a mechanism for their hypertrophic cardiomyopathy. The patients with hypertension or coarctation of the aorta had a left ventricular pressure load with resultant concentric hypertrophy rather than ASH. An association between coarctation of the aorta<sup>10</sup> or fixed left ventricular outflow obstruction<sup>1</sup> and hypertrophic cardiomyopathy has been noted previously in pediatric patients. Hypertrophic cardiomyopathy secondary to systemic hypertension is rare in our experience and is unusual in adult patients. Systemic hypertension in neonates may more frequently lead to hypertrophic cardiomyopathy than in adults perhaps related to the neonate's propensity for developing ASH and his disordered myocardial cell architecture<sup>2</sup>. The latter may also have contributed to the myocardial hypertrophy in the infants of diabetic mothers or their hypertrophy may be secondary to glycogen deposition *in utero* from chronic hyperinsulinemia and hyperglycemia. Our infants of diabetic mothers did not undergo cardiac catheterization but others have shown a subaortic gradient in these infants.<sup>1</sup> The infant in this series with tetralogy of Fallot is unusual and may represent a chance association. The develop-

ment of ASH secondary to right ventricular hypertrophy has been demonstrated in patients with tetralogy of Fallot but hypertrophic obstructive cardiomyopathy has not been documented. However our patient had SAM, mid-systolic closure, an unusual left ventricular angiogram and no ASH. The absence of a left ventricle to aorta pressure gradient may be related to the large ventricular septal defect in the subaortic position.

Previous studies<sup>11,12</sup> have pointed out the echocardiographic features of dynamic subpulmonic obstruction in infants with D transposition of the great arteries and an intact ventricular septum. The dilation of the right ventricle may contribute to the narrowing of the left ventricular outflow tract. The systolic anterior motion of the mitral valve and the systolic fluttering of the pulmonic valve may be secondary to the Venturi effect and to altered left ventricular geometry.<sup>11</sup> Infants with D transposition and intact ventricular septum who develop increasing cyanosis despite an adequate interatrial defect or who demonstrate hypercyanotic spells (similar to those seen in tetralogy of Fallot) may have dynamic left ventricular outflow obstruction.

In summary, the pediatric spectrum of hypertrophic obstructive cardiomyopathy has been illustrated in 21 patients. Echocardiography,



Fig 1 This composite photograph shows end diastolic (left) and end systolic (right) frames from cineangiography obtained from patients No. 17 (top row) and No. 18 (bottom row). The top row were obtained in an RAO projection while the bottom row were obtained in a PA projection. Each set of angiograms demonstrated systolic cavity obliteration of the left ventricle.

extremely useful in identifying left ventricular outflow obstruction or myocardial hypertrophy. The use of digitalis is probably contraindicated in these patients since this may exacerbate or create obstruction to outflow from the left ventricle. Further experience with hypertrophic cardiomyopathy and awareness of its coexistence with congenital heart disease may help elucidate the pathophysiologic mechanisms of this disorder.

### Summary

Twenty-one pediatric patients with echocardiographic and/or hemodynamic evidence of dynamic left ventricular obstruction are presented in order to examine the pathophysiologic mechanisms of this disorder. Neonates commonly had transient hypertrophic cardiomyopathy related to hypertension or to being infants of diabetic mothers. Infants with Down's syndrome of the great arteries sometimes developed signs of subpulmonic dynamic obstruction. Older children and adolescents had either classic findings of IHSS or concentric left ventricular hypertrophy. The spectrum of hypertrophic cardiomyopathy appears to be broader in pediatric patients than in adults.

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# The usefulness of radionuclide ventriculography for the identification and assessment of patients with coronary heart disease

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 Washington D C

Coronary arteriography and left ventricular angiography are often necessary to identify accurately the presence of coronary atherosclerotic heart disease and to assess its severity. As yet no noninvasive technique provides information of similar quality.

Recently cardiac imaging employing radionuclides has received considerable attention as a tool for identifying and evaluating coronary disease. When combined with exercise this approach appears particularly promising.<sup>1-3</sup> Studies utilizing 201 Thallium which like its analogue potassium is taken up by myocardium in proportion to blood flow have been most widely employed. Segments of relative hypoperfusion may be identified by detection of areas of reduced radioactivity within the myocardium.<sup>4</sup> An equally promising technique employs imaging of the left ventricular blood pool. An accurate representation of the left ventricle may be acquired using a computer interfaced scintillation camera during the first passage of a radioisotope through the heart or following equilibration of the radioactivity within the blood pool. The latter images are gated by means of an electrocardiographic signal and reconstructed in various

Table 1 Normal coronary arteriograms and normal left ventricle clinical features

Age	26-39 mean = 4 years 16 (84%) older than 39 years 9 men 10 women
Sex	
Reason for catheterization	
Chest pain (one had "Prinzmetal syndrome")	17
Ventricular fibrillation	1
Abnormal exercise ECG	1
Complicating conditions	
Mitral valve prolapse	8
Hypertension	3
Alcoholism	2
Diabetes	1

formats including left ventricular cineangiography.

Borer and associates<sup>5-7</sup> and other investigators have used rest and exercise radionuclide left ventriculography to demonstrate differences between the response of the left ventricle to exercise in normal persons and in patients with ischemic heart disease. As in the case during contrast left ventriculography, segmental contraction abnormalities are often present during the radionuclide examination.<sup>8-10</sup> Further segments which contract normally at rest may become abnormal during exercise. In addition to segmental abnormalities of left ventricular function, an abnormal response of the global ejection fraction may be detected. In contrast to normal subjects in whom the ejection fraction increases with exercise, it characteristically

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Table II Patients with occlusive coronary disease

	Number	Age		Sex		Angina	Myocardial infarction
		Range	Mean	Male	Female		
One vessel	11	31-68	54	11 (67%)	5 (33%)	13 (87%)	3 (27%)
LAD	10	42-68	53	6	4	9	1
RCA	4	31-68	53	3	1	3	1
CIRC	1	62		1	0	1	0
Two vessel	20	31-71	53	19 (95%)	1 (5%)	15 (75%)	13 (65%)
LAD+RCA	18	31-67	51	10	0	8	11
LAD+CIRC	11	38-71	56	9	0	6	3
RCA+CIRC	1	57		0	1	1	1
Three vessel	41	36-72	56	34 (83%)	7 (17%)	38 (88%)	24 (59%)
Total	76	31-72	55	63 (83%)	13 (17%)	60 (85%)	40 (53%)

cally fails to rise or declines in patients with coronary or left ventricular disease

The present study was undertaken to examine the usefulness of multiple gated acquisition of the left ventricular blood pool as a clinical tool for the identification of individuals with ischemic heart disease and for estimation of the severity of the disease process. Our experience with the technique when offered as a clinical service forms the basis for this analysis.

### Methods

Multiple gated acquisition of the left ventricular blood pool has been offered as a clinical service in the nuclear medicine laboratory of this hospital since late 1977. Exercise examinations were made available in March 1978. Approximately 1300 patients have been examined to date.

This analysis concerns the first 100 patients to undergo rest and stress examinations who (1) had coronary arteriography within six months of the study (within one month in 85%) (2) did not have valvular heart disease (3) had not had cardiac surgery and (4) did not have clinical myocardial infarction between arteriography and the radionuclide examination.

Nineteen patients had normal coronary arteriograms and normal left ventricular cineangiograms. Eight of this number had mitral valve prolapse but none had more than slight mitral regurgitation. Table I describes the clinical features of these patients.

Seventy-six individuals had a 50% or greater occlusion of at least one coronary artery. The distribution of these lesions is indicated in Table II along with certain clinical features of the patients.

Five patients had abnormal catheterization

studies but lacked 50% occlusion of a coronary artery. Four had abnormal left ventricular cineangiograms. The remaining patient had typical pain of ischemic heart disease, several less than 50% occlusions of the left anterior descending and circumflex coronary arteries and dramatically reduced velocity of flow through the partially occluded arteries and an adjacent apparently normal diagonal branch. The clinical, angiographic and radionuclide findings in these five patients are outlined in Table III.

**Radionuclide angiography.** Blood pool visualization was achieved by *in vivo* labelling of the patient's erythrocytes with 20 millicuries of 99m technetium using 17 milligrams of stannous pyrophosphate as the mordanting agent. Scintigraphic data were collected with a General Electric Porta Camera II C or with a G E Data Camera fitted with a high sensitivity parallel hole collimator, a hard wired zoomer and a cardiac shield were employed in the more recently performed studies. The cameras were interfaced to either an Informatek Simus III or IVB Computer. All patients were studied in the supine position using the left anterior oblique projection. The exact placement of the camera was individually chosen for each patient so as to best visualize the interventricular septum. This usually required an angle of 42 to 48 degrees. A 15 degree caudal inclination was employed so as to separate the left atrium from the left ventricle. In order to achieve maximal reproducibility between the resting and stress phases of the examination particular care was exercised to position the patient optimally with respect to the bicycle ergometer prior to the beginning of the study and not to move the patient between the two phases of the examination.



Table III Abnormal patients with less than 50% coronary occlusions

Age/sex	Clinical problems	Catheterization findings	Radionuclide centriculogram
1 49M	Atypical chest pain	Normal coronary arteries	Mild diffuse hypokinesis
2 53F	Atrial fibrillation	Diffuse hypokinesis of LV	FF fell from 0.51 to 0.50
3 60M	Atypical chest pain	Normal coronary arteries	Abnormal segmental wall motion, EF rose from 0.59 to 0.61
	Hypertension	Segmental hypokinesis of LV	EF fell from 0.59 to 0.61
4 41M	Atypical chest pain	30% occlusion RCA	Abnormal segmental wall motion, EF fell from 0.58 to 0.46
	PVC's	Segmental hypokinesis of LV	Severe diffuse hypokinesis
5 51M	CHF	Normal coronary arteries	FF fell from 0.17 to 0.09
	Typical effort angina	Severe diffuse hypokinesis of LV	Mild hypokinesis appeared with stress
		<50% occlusions in LCA and CIRC -low flow in IAD and a diagonal	EF fell from 0.58 to 0.60

Table IV Maximum level of exercise attained

	No	Watts	Heart rate	Double product
NI CA/NI LV	11	56 ± 8	108 ± 7	181 ± 15
NI CA/MVP	8	43 ± 6	106 ± 6	202 ± 16
Occlusive CAD				
One vessel	15	43 ± 9	106 ± 6	182 ± 11
Angina or ST	9	28 ± 8	102 ± 6	166 ± 11
No angina or ST	6	60 ± 14	111 ± 7	204 ± 21
Two vessel	20	53 ± 6	98 ± 4	153 ± 9
Angina or ST	10	40 ± 8	97 ± 5	167 ± 12
No angina or ST	10	56 ± 10	103 ± 6	145 ± 14
Three vessel	41	40 ± 3	100 ± 3	161 ± 7
Angina or ST	18	36 ± 4	98 ± 4	149 ± 8
No angina or ST	23	46 ± 5	101 ± 5	170 ± 14

Pavel and associates' modification<sup>11</sup> of the multiple ECG gated equilibrium data acquisition and processing technique of Borer and colleagues<sup>12</sup> was utilized. This involves the computer generation of 16 composite image matrices representing a single cardiac cycle. Each frame of this series contains the spatial isotopic distributional information describing the configuration of the blood pool during a specific phase of the cardiac cycle. Images of high statistical quality are obtained by collecting these data from many individual cycles and by programming the computer to create a series of multiple exposures. This series of images is displayed sequentially on the computer screen so as to simulate a beating heart. From the counts contained within the left ventricular end systolic and end diastolic regions of interest the computer calculated the ejection fraction.

Following placement of the ECG leads and an ECG line the patient was allowed to reach a baseline state with respect to pulse and blood pressure. When this was achieved the resting

phase of the examination was started. This involved the collection of a total of ten million counts and required approximately seven minutes.

Upon completion of this acquisition period patients were exercised in the supine position by means of a bicycle ergometer (Warren E Collins Braintree MA). The electrocardiographic signal (usually a modified Lead II) was displayed continuously on an oscilloscope. Strip chart recordings were obtained at intervals and whenever significant changes were observed. Blood pressure was measured during each minute of exercise by means of a sphygmomanometer. Exercise was begun at 25 watts (150 kilopond meters/minute) and increased by that amount every two minutes until the subject began to manifest fatigue, angina or electrocardiographic signs of ischemia. Data acquisition was then initiated and continued for three minutes during which the patient continued to pedal. Angina or progressive ST depression necessitated reduction in the work load prior to completion of the three minutes in some. In five it was necessary to terminate exercise during the final 30 to 60 seconds of data acquisition. Table IV indicates the level of exercise attained. Half of the patients with occlusive coronary disease had angina ST depression or both during exercise.

Each computer generated left ventricular cine angiogram was reviewed independently by two of us (J.L. and N.G.N.) without knowledge of the catheterization findings. Disagreement in the assessment of regional wall motion was resolved by joint review, often with reference to computer generated isocount lines which assist in the delineation of the edge of the left ventricular blood pool during various stages of the cardiac

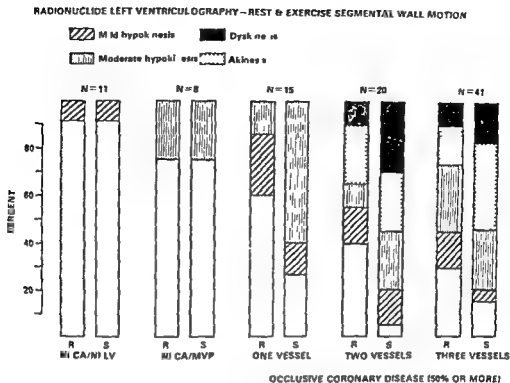


Fig 1 The bar graphs depict the per cent of patients in each diagnostic category with abnormality of segmental wall motion. The degree of the abnormality is indicated by variation in shading.

cycle. A judgment was made regarding the contractility of septal, apical, and lateral (or posterior) segments. A minimal abnormality was termed mild hypokinesis, and a definitely hypokinetic segment was termed severe hypokinesis. Akinesis<sup>10</sup> was used in cases of failure of the segment to contract and dyskinesis when outward or paradoxical motion occurred during systole.

### Results

**Normal coronary arteriograms and normal left ventriculograms.** At rest, ten of these eleven (91%) patients had normal segmental wall motion; slight hypokinesis was detected in one. No wall motion aberrations appeared during exercise in the 10 who were normal at rest. No deterioration occurred in the minimally abnormal ventriculogram of the eleventh (Fig 1).

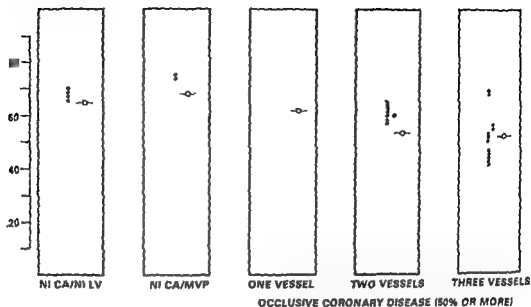
In these eleven patients, the left ventricular ejection fraction ranged from 0.56 to 0.75 at rest (mean  $\pm$  SEM =  $0.65 \pm 0.02$ ) (Fig 2, Table V). During exercise, it ranged from 0.50 to 0.74 (mean  $\pm$  SEM =  $0.67 \pm 0.02$ ). This increase is not significant. A rise in ejection fraction during exercise of three to 22% of the resting value was observed in seven patients. A fall of eight to 17% of the resting value occurred in the remaining

four patients (Fig 3). Two of these four were alcoholic and two were severely hypertensive. The latter two were receiving 160 and 240 mg of propranolol respectively for that problem.

**Mitral valve prolapse.** At rest, six of these eight (75%) patients had normal segmental wall motion. Severe hypokinesis was present in the apical segment in one instance and in the apical portion of the septal segment in another. During exercise, regional wall motion continued to be normal in the six who had normal findings at rest. A larger area of the left ventricle became hypokinetic during stress in the other two (Fig 1). Both had ischemic ST changes on the ECG during exercise, and one of the two experienced anginal pain. None of the six patients with normal regional wall motion had exercise-induced ST abnormalities, and only one had chest discomfort during stress.

The left ventricular ejection fraction at rest ranged from 0.59 to 0.79 (mean  $\pm$  SEM =  $0.68 \pm 0.03$ ) (Fig 2). During exercise, it ranged from 0.53 to 0.76 (mean  $\pm$  SEM =  $0.68 \pm 0.03$ ). In five of the eight, the change during stress ranged from a decline of four% to a rise of two% of the resting value. By contrast, one had an increase of 27%, one a decline of nine%, and

**RADIONUCLIDE LEFT VENTRICULOGRAPHY  
EJECTION FRACTION AT REST**



**Fig 2** The resting left ventricular ejection fraction for individual patients in each diagnostic category is depicted.

**Table V** Left ventricular ejection fraction

	NI CA/NI LV	NI CA/MVP	Occlusive Coronary Disease		
			One Vessel	Two Vessel	Three Vessel
Rest	65 ± 0.02	68 ± 0.03	62 ± 0.02	64 ± 0.03	52 ± 0.03
Exercise	67 ± 0.02	68 ± 0.03	59 ± 0.02	58 ± 0.03	48 ± 0.03*

< 0.01

p < 0.05

p < 0.01

one a decline of 10% of the resting value (Fig 3)

**Occlusive coronary disease**

**Single vessel occlusion** At rest six of the 15 (40%) patients had abnormal segmental wall motion. Slight hypokinesis was detected in four and severe hypokinesis was seen in the remaining two. During exercise stress the contraction pattern of five of the nine with normal resting wall motion and all four with mildly abnormal patterns deteriorated. Thus during stress normal segmental wall motion was present in four (27%), slight hypokinesis in two (13%), and severe hypokinesis in nine (60%) (Fig 1).

In these 15 patients the left ventricular ejection fraction at rest ranged from 0.49 to 0.74 (mean ± SEM = 0.62 ± 0.02) (Fig 2, Table V). During stress it ranged from 0.49 to 0.71 (mean ± SEM = 0.59 ± 0.02). This decline is significant ( $p < 0.01$ ) when the paired *t* test is applied. Three patients had a small rise in ejection

fraction (four to eight % of the resting value). Four had no change and seven had a fall of from one to 29% of the resting value (Fig 3). A decline of at least ten % of the resting value took place in four (27%) all of whom had occlusion of the left anterior descending artery.

**Double vessel occlusion** At rest twelve of (60%) patients had abnormal segmental contraction. Slight hypokinesis was present in three and severe hypokinesis was present in two. Five had akinesis and two had dyskinetic segments. Seven of the eight which were normal at rest deteriorated. Thus during exercise stress six patients (30%) had dyskinetic segments, five (25%) had akinesis, five had severe hypokinesis (25%), and three (15%) had mild hypokinesis. One (5%) remained normal (Fig 1).

In these patients the resting ejection fraction ranged from 0.30 to 0.74 (mean ± SEM = 0.54 ± 0.03). In six it was less than 0.50 (Fig 2, Table V). During exercise stress it ranged from 0.25 to 0.71

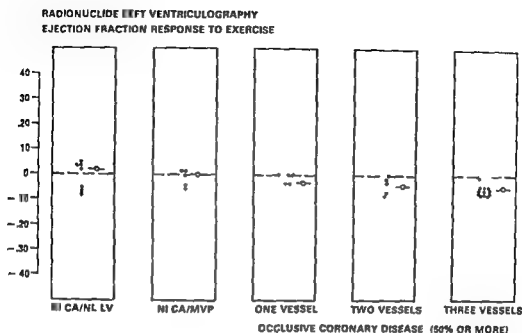


Fig 3 The response in left ventricular ejection fraction to exercise for individual patients in each diagnostic category is depicted.

(mean  $\pm$  SEM =  $0.50 \pm 0.03$ ) This decline is significant ( $p < 0.05$ ). Three patients (15%) had an increase in ejection fraction during stress of eight to 17% of the resting level two (10%) had no change and 15 (75%) had a decline of from two to 29%. The decline amounted to ten % or more of the resting value in nine (45%) (Fig 3).

**Triple vessel occlusion:** At rest 29 of 41 (71%) patients with occlusive disease in all three major vessels had abnormal wall motion at rest. Dyskinesia was present in four (10%), akinesis in seven (17%), severe hypokinesia was present in 12 (29%) and mild hypokinesia was present in six (15%). During exercise stress six (15%) remained normal. Dyskinesia was present in seven (17%), akinesis was present in 15 (37%), severe hypokinesia appeared in eleven (27%) and mild hypokinesia was apparent in two (5%) (Fig 1).

The resting left ventricular ejection fraction in 40 patients ranged from 0.19 to 0.81 (mean  $\pm$  SEM =  $0.52 \pm 0.02$ ). In 17 patients (43%) this value was below 0.50 (Fig 1, Table V). One patient had a ventricular aneurysm. His left ventricular silhouette exceeded the area available to the computer for the ejection fraction calculation. During stress the ejection fraction in the 40 in whom it could be calculated ranged from 0.10 to 0.82 (mean  $\pm$  SEM =  $0.48 \pm 0.03$ ). The decline during exercise is significant ( $p < 0.001$ ). In 12 patients (29%) a rise in ejection fraction of

one to 35% of the resting value accompanied exercise and in 29 a fall of one to 65% was detected. In five (13%) the increment was at least 10% of the resting value while in 17 (43%) the decrement was at least that amount (Fig 3).

### Discussion

The radionuclide angiographic findings obtained in our laboratory are consistent with the experience previously reported in patients with coronary heart disease.<sup>1,2</sup> Regional wall motion abnormal at rest in 62% became abnormal in an additional 24% so that during exercise abnormality was detected in 86% of patients. Furthermore the left ventricular ejection fraction characteristically failed to rise significantly and with few exceptions fell during exercise often quite dramatically.

With a single exception segmental wall motion was normal both at rest and during exercise in the 11 patients who had no angiographic abnormality of their coronary arteries or left ventricle. A rise in global ejection fraction reported to be characteristic of normal individuals<sup>2,3</sup> was observed in seven of the 11. The lack of a normal response in four patients and the relatively small increase in several of the others probably reflects the fact that cardiac catheterization was requisite for admission to this study. Thus patients whose noninvasive studies were abnormal or who had impressive signs and symptoms of heart disease

were selected for catheterization. For instance of the four whose ejection fraction fell with exercise, two were alcoholic and two were severely hypertensive. One of the alcoholic patients had had an episode of ventricular fibrillation and the two hypertensive subjects were receiving substantial amounts of propranolol daily.

The findings in our eight patients in whom mitral valve prolapse was documented by left ventriculography are of interest. Two had hypokinesia at rest which became somewhat more widespread during exercise. It is noteworthy that these two individuals had ischemic ST changes during exercise. None of the other six exhibited such changes. Furthermore, a substantial increase in the global ejection fraction was observed in only one of the eight. The factors discussed above in relation to the selection for catheter study of the 11 individuals with normal coronary arteriograms and normal left ventriculograms may apply here as well. Our small group is certainly not representative of the majority of patients with this disorder. They were older (47 to 59 years of age) and they all had experienced chest discomfort more or less suggestive of ischemic heart disease. On the other hand, other investigators have encountered similar abnormalities in the radionuclide ventriculograms of patients with mitral prolapse<sup>12, 13</sup> and left ventricular dysfunction has been frequently detected at cardiac catheterization in these pa-

tients.

The specificity of the technique can not be estimated from our data. Among several of our 11 patients who had normal angiographic studies, there are reasons to suspect the possibility of an abnormal left ventricular myocardium as a result of hypertension, drug therapy, alcoholism, or other causes. It is encouraging that despite the presence of such factors, ten of the 11 had normal regional left ventricular wall motion both at rest and during stress. The single exception had a minimal abnormality. Because of the manner in which our normal patients were selected, it is not surprising that in four we did not find the rise during exercise of the global ejection fraction characteristic of subjects selected for study by other investigators, because they were free of all signs of heart disease.

As we attempted to make diagnostic decisions in individual cases, we became aware of certain pitfalls. Visual review of the left ventricular cineangiograms for the detection of regional wall

motion abnormality requires a subjective judgment by the reviewer. This is true of most radiographic and angiographic diagnostic procedures. Fortunately, many cardiologists and radiologists are accustomed to studying left ventricular wall motion by means of contrast angiography. We found that most abnormalities were obvious even to the inexperienced and we found that subtle changes could be recognized confidently with some experience.

The use of the response to exercise of the global ejection fraction in interpretation of an individual patient's study is a more troublesome problem. In order to interpret the observed response, one needs to know the error of the measurement. Since the difference between the rest and stress examination includes whatever inaccuracies are present in both studies, the observed response to exercise is subject to a potential error as great as the sum of the errors of measurement in two examinations. Thus, the actual response to exercise may be exaggerated, obscured, or in the worse case, reversed in direction. Since it seems unlikely that these estimations are more accurate than  $\pm 5\%$  of the observed value<sup>14, 15</sup>, we have chosen to regard a change of 10% of the resting value as probably significant.

In addition to errors of measurement, the amount of exercise undertaken must be important in determining the amount and direction of change of the ejection fraction response. The data of Borer and associates<sup>1</sup> suggests that characteristic ejection fraction changes occur during submaximal exercise, but whether or not the patient with coronary disease exercises sufficiently to produce ischemia seems certain to be important. Berger and associates<sup>4</sup> and Frischknecht and colleagues<sup>6</sup> found that the ejection fraction fell far more often in patients with coronary disease when exercise was adequate to produce electrocardiographic evidence of ischemia. Only one of the seven coronary patients in our series who increased his ejection fraction by at least 10% of the resting value had ST changes suggesting ischemia, an observation which seems to support the position that exercise to the point of ischemia is important.

Brady and associates<sup>1</sup> recently reported that five of the six false negative examinations encountered in their study of 86 coronary patients were observed in the 15 who did not have angina or ischemic ST change and who did not reach a rate pressure product of 250. The ejection

fraction increased by an average of 0.12 in these five patients.<sup>1</sup> Eleven of our 76 coronary patients had normal segmental wall motion during stress. Six were among the 39 (15%) who were inadequately exercised by the criteria of Brady et al and five were among the 37 (14%) who were adequately stressed. Although our data do not confirm Brady's experience, we consider that the level of stress reached is very important. It remains to be determined what level of stress is adequate to allow a confident reading of normal.

The effect of the beta blocking agents on the results of this examination are also worthy of consideration. Borer and associates<sup>20</sup> have shown that acute intravenous propranolol does not obscure the exercise induced decline of the left ventricular ejection fraction in coronary patients. Wisenbarg and colleagues<sup>21</sup> demonstrated a smaller increment in ejection fraction during bicycle exercise in normal subjects receiving oral propranolol and a smaller decrement in coronary patients during propranolol administration as compared to their performance prior to receiving the agent. Furthermore, it seems likely that since administration of propranolol allows angina patients to undertake a greater amount of muscular work before the appearance of symptoms or ECG changes,<sup>22</sup> some patients will develop leg fatigue and be protected from developing ischemia by beta blockade. We therefore recommend the discontinuation of propranolol before a radionuclide ventriculogram. It is however often judged by the referring physician to be unsafe or impractical. Therefore 41 of the 76 coronary patients in this study were receiving this agent. Five of the eleven with normal segmental wall motion during stress were not receiving propranolol, two were receiving 160 mg per day or more and four were receiving lesser amounts. Although we postulate a protective effect from this drug, our data do not establish this. We do view with some skepticism a normal examination in patients receiving this agent.

The radionuclide ventriculogram appears to be useful not only in identifying patients with heart disease but also as a means of assessing its severity. The resting study provides insight into left ventricular function quite comparable to that obtained from contrast studies.<sup>23</sup> The response of the left ventricle to exercise appears to provide additional information regarding left ventricular reserve and the amount of left ventricle jeopardized by occlusive disease.<sup>24</sup> Our study does not

provide quantitative information in this regard but is consistent with this view. An ejection fraction less than 0.50 was present in 24 (32%) of our coronary patients. Twenty two of the 24 (92%) had severe occlusive disease in both the left anterior descending and in the right coronary artery. Twenty (83%) had a clinical history of myocardial infarction. Eight additional patients had a fall in their ejection fraction during exercise to a level below 0.50. Of those eight, seven had multivessel disease. A decline of at least ten % of the resting ejection fraction took place in 30 (39%) of the patients with coronary disease. Of these 26 (87%) had multivessel coronary disease and the remaining four had proximal occlusive disease in the left anterior descending artery.

Unfortunately, a less abnormal study does not preclude severe arterial disease as estimated by coronary arteriography. An increase in ejection fraction greater than ten% of the resting value and normal left ventricular wall motion were found in five of 41 (12%) of patients with occlusions of at least 50% in each of the three major branches of the coronary arteries. Oddly, such normal studies were not obtained in the 20 patients with two occluded vessels or in the 15 patients with single vessel disease. Review of these radionuclide ventriculograms and recalculation of the ejection fraction revealed no technical errors. Perhaps greater exercise stress would have disclosed latent abnormality. One of the five had no vessel judged at arteriography to be occluded by as much as 75% and a second had an occlusion of such a magnitude only in the right coronary. The other three had 75% or greater occlusions in multiple vessels. It remains to be determined whether this apparent aberration results from an error in the performance or the interpretation of either the radionuclide ventriculogram or the coronary arteriograms or whether it identifies a small group of patients with unusually competent collateral vessels or whether there is some other explanation.

Based on the experience herein reported and a total of some 1,300 examinations in our laboratory to date, we feel that rest and exercise radionuclide left ventriculography is a valuable diagnostic modality for clinical application. Much remains to be learned regarding its sensitivity and specificity. Furthermore, intriguing questions remain regarding its use in assessing the physiologic behavior of the left ventricle and the coronary circulation.

## Summary

To assess the usefulness of radionuclide angiography for the identification and evaluation of patients with coronary heart disease, we analyzed 100 consecutive patients who had undergone that examination and coronary arteriography.

Regional wall motion abnormality during exercise was detected in 65 of 76 (86%) patients with occlusive coronary disease and in one of 11 (9%) with normal coronary arteries and normal left ventriculograms.

The changes in the left ventricular ejection fraction in response to exercise were not helpful for the identification of individual patients with coronary disease since changes were often small and within the error of the technique. Substantial decline of the ejection fraction during exercise indicated multivessel disease or severe proximal left anterior descending artery occlusion.

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# Experimental and laboratory reports

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## Left ventricular cavity obliteration hemodynamic behavior of the postextrasystolic beat

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In postextrasystolic beats there is an increase of myocardial contractility that leads to an increase of intraventricular and aortic pressures and to an augmented ejection<sup>1</sup>

Brockenbrough and associates<sup>2</sup> have shown that in patients with idiopathic hypertrophic subaortic stenosis (IHSS) there is a paradoxical decrease of the aortic pressure in the postextrasystolic beat (PEB)

Left ventricular cavity obliteration (LVCO) is an angiographic entity characterized by a marked reduction in the ventricular cavity during contraction. This entity is associated with states of "hypercontractility" especially those presenting with left ventricular hypertrophy as in idiopathic hypertrophic subaortic stenosis (IHSS). However, in some cases the ventricular hypertrophy is not prominent and the most significant feature is the hypercontractile state. In this regard a similar situation has been induced in experimental dogs during inotropic stimulation and hemorrhagic shock.<sup>3</sup>

Recently a similar behavior has been reported in the PEB in patients with LVCO without obstruction to the left ventricular outflow tract

and in patients with IHSS pointing to a close similarity between the two conditions.<sup>4</sup>

In the present work the changes in aortic and ventricular pressure in the PEB are analyzed in 13 cases of LVCO without obstruction to the left ventricular outflow tract and substantial differences from their behavior in IHSS are found.

### Material and methods

Thirteen patients (six males and seven females) ranging in age between 12 and 62 years (mean 37.7 years) with LVCO in their left ventriculograms were studied. In 11 cases no pressure gradient could be found either in basal conditions or after amyl nitrite administration. The remaining two cases showed pressure gradients of 18 and 20 mm Hg respectively after amyl nitrite. In all cases roentgenographic and electrocardiographic data were analyzed. Echocardiograms were available in 10 cases.

The hemodynamic studies were performed with light sedation and no patient was receiving any cardioactive medication. Pressures were recorded before angiography was performed. To analyze pressures in the PEB any extrasystole preceded by at least two sinus beats during the recording of intraventricular pressure was selected. A similar analysis with aortic pressure was performed in four cases.

The left ventriculograms were performed in the right anterior oblique projection with the use of 0 cc of roentgen contrast. LVCO was considered when

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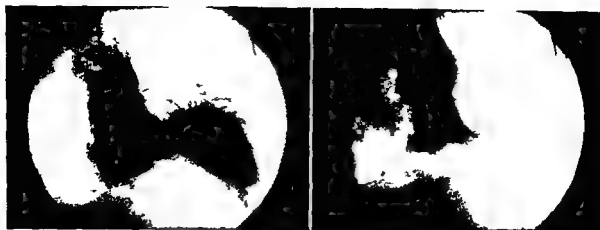


Fig 1 Left ventriculogram in the right anterior oblique projection. Left panel diastole. Right panel systole. Note the systolic reduction of the cavity with "sand glass" morphology. Mitral valve prolapse is also seen.

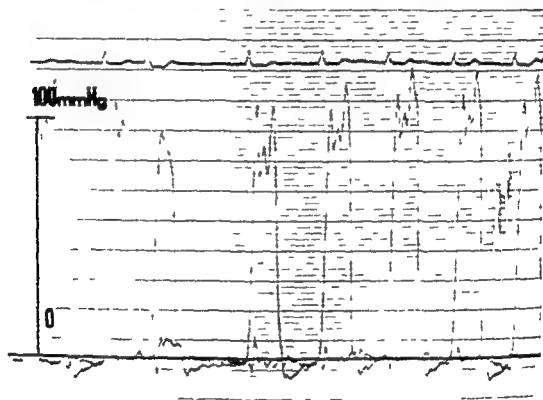


Fig 2 Simultaneous recording of left ventricular and pulmonary wedge pressures. In the postextrasystolic beat (fourth beat) there is a decrease of 10 mm Hg in the left ventricular systolic pressures.

apical intracavitary space disappeared during ventricular systole (Fig 1). Ejection fraction, circumferential fiber shortening rate, and mean normalized systolic ejection rate were calculated from the single plane right anterior oblique projection. Coronary arteriography with the Sones technique was performed in eight cases.

## Results

**Clinical features.** Ten patients (77%) presented with chest pain, four (30%) with dyspnea, three (23%) had palpitations, and two (15%) presented with sustained hypertension.

**Electrocardiograms.** Nine cases (69%) showed left ventricular hypertrophy; two (15%) a pattern

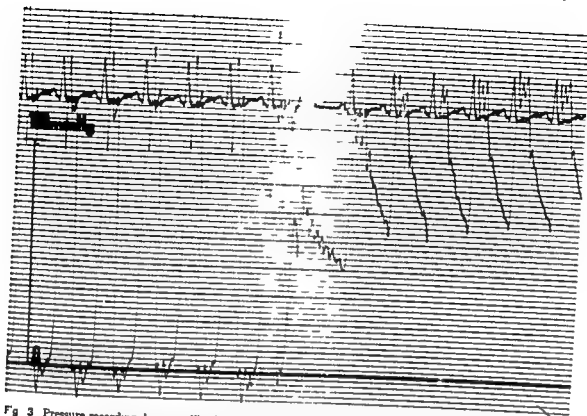


Fig 3 Pressure recording during pullback from left ventricle to aorta. The eighth beat is an extrasystolic and corresponds to aortic pressure. The following beat (postextrasystolic beat) has an aortic pressure 12.5 mm Hg lower than the subsequent beats. Neither transvalvular nor subvalvular aortic gradients are present.

Table 1 Summary of echocardiographic and hemodynamic data

Patient	Age	Echo data			Hemodynamic data					Angiographic data	
		LVH	SAM	MP	LVEDP	MV (sec)	MNSER (sec)	EF (%)	Subaortic gradient		
1	36				10	1.99	3.40	72	0		
2	37	C	Yes	No	8	2.02	3.33	92	0		
3	63	No	No	No	8	2.03	3.60	93	0		
4	16	No	No	Yes	8	3.80	6.33	86	0		
5	50	C	Yes	No	10	5.33	7.23	94	18 mm Hg post nitrate	MP	MR
6	43				4	2.88	4.16	91	0		
7	30	A	Yes	No	8	4.54	5.63	92	0		
8	12	A	Yes	No	8	3.09	4.0	8	0		
9	45	A	No	No	10	1.85	3.30	80	0		
10	43				20	2.83	4.62	86	0		
11	19	No	Yes	No	10	3.96	6.07	90	0		
12	13	A	No	Yes	10	5.20	6.00	92	0		
13	30	No	Yes	No	9	5.31	6.63	91	0	MP	MR
Mean					9	3.45	5.00	88.53	0		
SD					4.51	1.33	1.39	5.78			

Echocardiogram was not available in Cases 1, 6, and 10. Coronary arteriography was not performed in Cases 4, 7, 8, 12, and 13. Abbreviations: LVH = left ventricular hypertrophy; C = concentric; A = asymmetric; SAM = systolic anterior motion of mitral valve; MP = mitral prolapse; MR = mitral regurgitation; LVEDP = left ventricular end-diastolic pressure; MV = mitral velocity of circumferential fiber shortening; MNSER = mean normalized ejection rate; EF = ejection fraction; LAD = left anterior descending coronary artery.

of intraventricular block and one (7%) showed a pattern of old myocardial infarction

**Echocardiograms** The recording was available in 10 cases. Systolic anterior motion of the anterior leaflet of the mitral valve (SAM) was found in six (60%); asymmetric septal hypertrophy was found<sup>12</sup> in four (40%); symmetric hypertrophy in two (20%); and mitral valve prolapse appeared in two (20%).

**Hemodynamic data** Only in two cases could a subaortic gradient of 18 and 20 mm Hg be demonstrated after the inhalation of amyl nitrite. The left ventricular end diastolic pressure at rest ranged from 0 to 20 mm Hg; mean 9 mm Hg. A postextrasystolic beat at intraventricular level was recorded in all cases and also at the aortic level in four cases. There was a decrease in the systolic pressure peak (from 2 to 25 mm Hg; mean 8.5 mm Hg) in every case during the PEB both in the left ventricle and aorta (Figs 2 and 3).

**Left ventriculograms** Systolic reduction of apical intracavitary space (Fig 1) was noted in all the patients. In two cases a mitral valve prolapse was observed and mitral regurgitation was seen in six. The ejection fraction ranged from 0.72 to 0.94 (mean 0.89); the circumferential fiber shortening rate between 1.85 and 5.33 (mean 3.45). The mean normalized systolic ejection rate ranged between 30 and 7.23 (mean 5.0).

**Coronary arteriography** Left dominance was found in three of eight patients studied. Obstructive lesions were found in one case.

Table I summarizes echocardiographic hemodynamic and angiographic data following an individual display.

## Discussion

Brockenbrough and associates<sup>1</sup> considered the increase of pressure gradient in the PFB in IHSS as a phenomenon resulting from the obstruction to the left ventricular outflow tract (generated by the increase of contraction in the PEB). In this situation there is a decrease of aortic and supra-stenotic ventricular chamber pressures whereas in the substenosis chamber the ventricular pressure increases.

There are some common features between IHSS and LVCO without obstruction such as the angiographic left ventricular picture, the existence of intraventricular gradient pressure and the echocardiographic SAM. Ruzner and co-

workers<sup>1</sup> consider the LVCO as a contraction abnormality that may be seen in a wide spectrum of diseases with left ventricular hypertrophy—for example the IHSS—they also believe that LVCO in itself could explain the PEB phenomenon as well as the pressure gradient between obliterated and normocontractile or hypercontractile portions.<sup>8</sup> Our cases of LVCO without obstruction presented with a hypercontractile state as may be seen in the contractility indices derived from the left ventriculogram. All cases showed a decrease in left ventricular systolic pressure in the PFB, a differential feature from IHSS. This finding could be attributed to a pressure recording made above an unnoticed obstruction to the left ventricular outflow tract; however, several data make this hypothesis unlikely. (1) In all cases a pullback from apex to aorta was performed at rest and after nitrite inhalation and only in two cases could a pressure gradient be demonstrated.<sup>13</sup> In spite of the evidence that the catheter during the pullback had been placed below the usually obstructing portion in the IHSS in all cases the left ventricular systolic pressure was constant and identical to the aortic pressure during the whole recording. (3) Only two of the 10 cases with echocardiograms showed both asymmetric septal hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve, whereas in two cases none of these could be demonstrated.

In LVCO without obstruction there may appear artifactual intraventricular pressure gradients due to catheter entrapment in the obliterated portions<sup>14</sup> or true gradients between obliterated and non obliterated portions of the left ventricle.<sup>8</sup> Sophisticated catheterization techniques such as left atrial catheterization and pullback from the left ventricle to the left atrial cavity<sup>14</sup> would be needed to adequately demonstrate these facts. These maneuvers were not performed in our patients so there is no clear evidence of the behavior of ventricular systolic pressure in the PEB and if the obliterated cavity behaved in the same way as the non obliterated cavity then the decreased pressure was transmitted to the aorta since no left ventricular outflow tract obstruction existed. The decrease of the aortic systolic pressure in the PEB is a similar feature both of IHSS and LVCO without obstruction but the decrease of intraventricular pressure in LVCO clearly indicates that different mechanisms are involved i.e.—obstruction to the left

ventricular outflow tract is the most probable explanation for the decrease in aortic pressure and the increase in intraventricular pressure in IHSS while in LVCO the decrease in aortic pressure is secondary to the decrease in intraventricular pressure.

To understand the reasons for the decrease in intraventricular pressure in the PEB in patients with LVCO without obstruction two mechanisms could be invoked. (1) The existence of phenomena similar to the ones in IHSS but at a lower level between obliterated and nonobliterated portions where gradients could exist and be increased by an augmented contraction. (2) Beck and colleagues<sup>17</sup> think that the decrease in intraventricular pressure in the PEB is a common finding in normal hearts and could be explained by the progressive emptiness of the systemic vascular bed during the postextrasystolic pause. Left ventricular ejection would be performed against low systemic resistances thus resulting in a potentiation of contraction comparatively less than the reduction in the impedance of the systemic vascular bed and therefore resulting in a decrease of the intraventricular pressure. However, patients with ventricular dysfunction show postextrasystolic potentiation of aortic pressure.<sup>18</sup> This fact has been explained by the increased aortic impedance in these patients with decreased cardiac output and stroke volume associated with higher peripheral vascular resistances.<sup>19</sup>

The cases with obstruction to the left ventricular outflow tract would present with an inverted behavior since the left ventricular ejection fraction would be against a fixed resistance which would result in an increase of the intraventricular pressure. In this regard some authors<sup>2</sup> have found in IHSS patients an inverse correlation between the subaortic gradient and the diastolic pressure both in sinus beats and in PEB. In patients with LVCO without obstruction the postextrasystolic ventricular pressure would be the same as in normal hearts although somewhat increased by the decreased compliance and the decreased diastolic filling.

**Clinical implications.** Our data show that the patients with LVCO without obstruction like the patients with IHSS may exhibit a decrease of aortic systolic pressure in the PEB but there is also a decrease of intraventricular pressure. This feature would distinguish the cases of LVCO with

obstruction from those without obstruction to the left ventricular outflow tract.

### Summary

Thirteen patients with angiographic left ventricular cavity obliteration are analyzed. No transvalvular or subvalvular gradients were present except in two cases with a mild gradient after amyl nitrite inhalation.

The commonest clinical features were chest pain (60%) and dyspnea (23%). Electrocardiographically proved left ventricular hypertrophy (70%) was prominent. The echocardiograms showed asymmetric septal hypertrophy (40%), symmetric hypertrophy (20%), systolic anterior motion of the anterior leaflet of the mitral valve (60%) and mitral valve prolapse (20%).

In all the patients changes in systolic intraventricular pressure in the post extrasystolic beat were evaluated and a decrease in intraventricular pressure was found in every case. In the four cases with extrasystoles recorded in the aorta a similar decrease of aortic pressure was found. This behavior is completely different in the hypertrophic cardiomyopathy with obstruction to the left ventricular outflow tract where there is an increase in intraventricular pressure and a decrease in aortic pressure in the postextrasystolic beat.

Left ventricular cavity obliteration is an angiographic phenomenon which is common in hypertrophic states being an unusual finding in hypertrophic cardiomyopathy. In cases without obstruction to the left ventricular outflow tract the decrease in aortic pressure is caused by a different mechanism than the one involved in cases with obstruction. In cases without obstruction the decrease in post extrasystolic aortic pressure corresponds to a decrease in intraventricular pressure whereas in subaortic stenosis there is an increase both of intraventricular pressure and gradient with the subsequent decrease in aortic pressure.

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# Myocardial blood flow as a determinant factor in the electrical stability of the myocardium

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Acute myocardial infarction is followed by a period of electrical instability of the myocardium. In experimental animals this electrical instability can be measured by determining the threshold for ventricular fibrillation. Previous experiments have shown that ventricular fibrillation threshold (VFT) transiently decreases after acute coronary artery ligation for a period of 5 to 20 minutes in both ischemic and remote nonischemic areas of myocardium. The transient decrease in ventricular fibrillation threshold in remote nonischemic areas of myocardium has raised questions regarding the mechanisms by which the VFT is lowered following coronary artery occlusion. The present study was undertaken to determine the relationship between regional myocardial blood flow and electrical stability of myocardium as measured by ventricular fibrillation threshold during subendocardial and transmural ischemia.

## Materials and methods

Twelve adult mongrel dogs weighing 20 to 35 kilograms were anesthetized with intravenously administered sodium pentobarbital 30 mg/Kg body weight. The animals were intubated and ventilated with a Harvard respirator using room air. The heart was exposed through a left lateral

thoracotomy and suspended in a pericardial cradle. Heart rate was kept constant by crushing the sinus node and pacing from the atria with bipolar plunge electrodes at a constant cycle length of 400 msec (150 beats/minute). Systemic arterial pressure was continuously monitored by means of a catheter placed in the central aorta utilizing a Statham P23Db pressure transducer. A section of the proximal left anterior descending coronary artery was isolated and an electromagnetic flow transducer screw occluder and snare were placed on the artery, the flow transducer being more proximal and the snare more distal (Fig 1). Arterial pH was maintained between 7.34 and 7.45 by regulating the respiratory rate and tidal volume settings of the Harvard respirator. Arterial PO<sub>2</sub> was kept above 60 mm Hg with supplemental oxygen and body temperature was maintained between 36 to 38 °C with the use of a heating blanket.

The fibrillating electrodes were Teflon coated stainless steel diameter 0.01 inch threaded through a 22 gauge hypodermic needle. The terminal portion of this wire was stripped of insulation for 3 mm and made into a hook. A pair of such hook electrodes were placed 8 mm apart in the subendocardium and subepicardium of an area supplied by the left anterior descending (LAD) and left circumflex (LCX) coronary arteries. The position of the electrodes was confirmed by recording unipolar and bipolar electrograms from these electrodes and also by localizing the tips of the electrodes by myocardial dissection at the end of the experiments.

## Ventricular fibrillation threshold determina-

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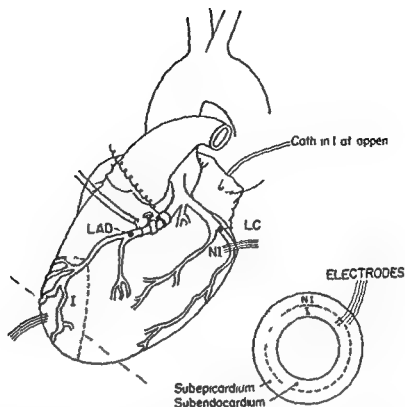


Fig 1 Diagrammatic representation of the experimental model. Note the position of the snare screw occluder and flow probe on the left anterior descending coronary artery (LAD). LC = left circumflex artery. I = ischemic area. NI = non ischemic area. Position of the electrodes is shown in the cross sectional area.

Table 1 (n = 12)

	LAD ENDO VFT	LAD ENDO MBF	LAD EPI VFT	LAD EPI MBF	LCX ENDO VFT	LCX ENDO MBF	LCX EPI VFT	LCX EPI MBF	LAD ENDO/ EPI	LCX ENDO/ EPI
Mean	16.1	79.6	15.9	81.0	18.8	79.7	15.5	77.7	9.1	18
± SD	3.7	15.6	4.3	13.9	6.3	14.2	3.5	10.0	10	0.14

Control values for ventricular fibrillation threshold (VFT) and myocardial blood flow (MBF) in the left anterior descending coronary artery (LAD) region and left circumflex coronary artery (LCX) regions.

tion. The hook electrodes were connected to a constant current source which delivered a train of 20 pulses each 2 msec in duration and 8 msec apart for a total duration of 200 msec. The pulse train was synchronized with Lead II surface electrocardiograms and was programmed to begin 50 msec after the onset of the last paced QRS complex of every twelfth paced beats. Following delivery of the pulse train pacing was interrupted for one basic cycle length and then resumed. The strength of the pulse train was increased by 1 milliamp (mA) increments until ventricular fibrillation (VF) occurred. The least amount of current required to produce VF measured as the voltage drop across a known 1 k resistor was taken as the ventricular fibrillation threshold. The heart was then defibrillated with 10 to 20

watt seconds of direct DC current within 10 seconds of VF. A 15 minute recovery period was permitted between consecutive VFT determinations. VFT determination was repeated until consecutive measurements agreed within 10 percent of each other.

**Myocardial blood flow measurements.** After the control VFT determinations, myocardial blood flow (MBF) was measured using the radioactive microsphere technique. In this technique 0.05 to 0.15 ml ( $2 \times 10^5$  spheres) of  $^{14}$ C carbonized microspheres ranging in size from 7 to 10  $\mu$  and labelled with Sc, Nb, Ce, or Sr were injected through the left atrial catheter and were sampled from the femoral artery at a constant withdrawal speed using a Harvard constant infusion pump. At the end of the experiment portions

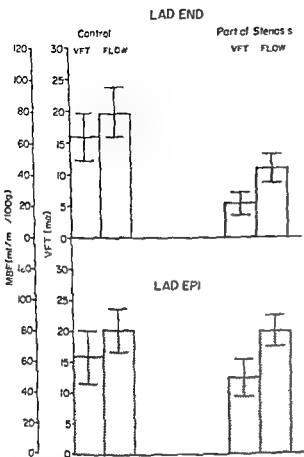


Fig 2 Ventricular fibrillation threshold (VFT) and myocardial blood flow (MBF) in the endocardium (END) and epicardium (EPI) of the left anterior descending coronary artery (LAD) distribution after partial stenosis of LAD. Note with partial stenosis there is a selective decrease in MBF in the LAD subendocardium with an associated fall in VFT. No significant change is seen in MBF and VFT in the LAD epicardium.

of the myocardium surrounding the electrodes were removed and were sectioned into subendocardium and subepicardium. Tissue samples, blood blanks and standards were counted for 10 minutes in a scintillation counter. Blood flow to the various segments of the myocardium was determined by knowing the withdrawal rate, counts in the blood sample and counts in the tissue.

**Partial stenosis of the left anterior descending artery (LAD).** Following determination of control VFT and myocardial blood flow in 12 dogs, a 15 second occlusion of the LAD was performed to evaluate the reactive hyperemic response. The screw occluder was then tightened until all the hyperemic response was abolished and the resting flow was reduced 25 to 30 per cent from the control values. VFT and MBF measurements

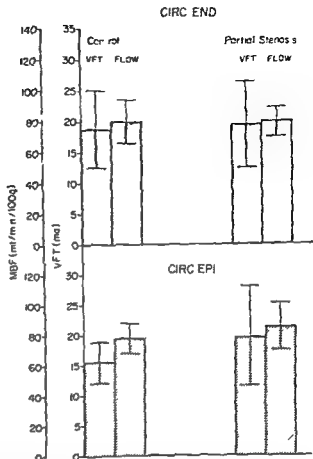


Fig 3 Ventricular fibrillation threshold (VFT) and myocardial blood flow (MBF) in the endocardium (END) and epicardium (EPI) of circumflex region following partial stenosis of left anterior descending coronary artery. No significant change in MBF or VFT from control values is demonstrated in the circumflex region.

were repeated after a 15 minute equilibration period.

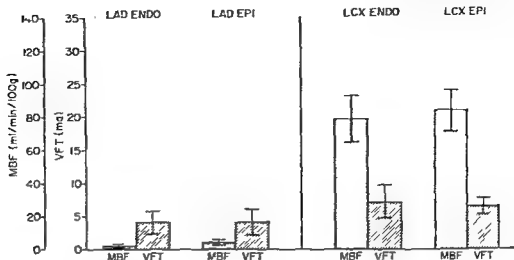
**Ligation of the left anterior descending coronary artery (LAD).** The LAD artery was ligated in 12 dogs by tying it off with a silk suture proximal to the first diagonal branch. Following a five minute equilibration period VFT was determined and myocardial blood flow was measured by injecting a second set of microspheres.

## Results

VFT and myocardial blood flow were not significantly different in any of the four regions during the control period (Table I). With partial stenosis myocardial blood flow as determined by the microsphere technique showed a selective decrease of 44.7 per cent ( $p < .001$ ) in the LAD subendocardium accompanied by a decrease of 66.6 per cent ( $p < .001$ ) in VFT values. In the LAD subepicardium region there was no signifi-



**MYOCARDIAL BLOOD FLOW AND VENTRICULAR FIBRILLATION THRESHOLD  
WITH LEFT ANTERIOR DESCENDING CORONARY ARTERY OCCLUSION**



**Fig 4** With occlusion of LAD both VFT and MBF fell in the LAD region. There is also a decrease in VFT in the circumflex region without an associated change in MBF

cant changes in myocardial blood flow or VFT (Fig 2) During the partial stenosis of LAD in the circumflex regions myocardial blood flow and VFT values were unchanged from control values (Fig 3)

Following LAD ligation in 12 dogs a decrease in VFT was found in all four regions. The LAD subendocardium VFT fell 75.6 per cent from control values which was not significantly different from the decrease found during partial stenosis. In the LAD subepicardium also showed a similar decrease with the ligation 74 per cent ( $p < 0.001$ ). Myocardial blood flow during ligation of LAD decreased in the LAD subendocardium and subepicardium by 98.2 per cent and 91 per cent respectively (Fig 4). In the circumflex endocardium and subepicardium the myocardial blood flow was not significantly changed following ligation of LAD. However the VFTs in circumflex subendocardium and subepicardium decreased 62.2 per cent and 59.1 per cent respectively ( $p < 0.001$ ) (Fig 4).

#### Discussion

The present study has demonstrated three distinct patterns for ventricular fibrillation threshold in relationship to myocardial blood

2 With ligation of the left anterior descending coronary artery there is a decrease in ventricular fibrillation threshold in both the subendocardial and subepicardial regions of myocardium. The decrease in VFT following ligation is associated with a reduction in myocardial blood flow.

3 Immediately following left anterior descending coronary artery ligation ventricular fibrillation threshold in remote nonischemic areas of myocardium also shows a significant fall while MBF is unaltered.

The finding that VFT is directly related to myocardial blood flow following partial stenosis, although not previously reported, is not unexpected. Partial stenosis as produced in the current experiments results in a selective reduction in subendocardial blood flow. Previous studies have shown a decrease in myocardial high energy phosphates following ischemia as well as a loss of intracellular potassium.<sup>11</sup> Resting membrane potential shifts toward zero and the fast current is unactivated. The slow inward current will still, however, be active<sup>12</sup> and along with a low resting membrane potential will tend to delay intraventricular conduction. The delay in intraventricular conduction predisposes toward reentry which may manifest itself as a ventricular tachycardia or fibrillation. The low VFT in the area can thus be explained on the basis of the biochemical and electrophysiological changes that occur with ischemia.

A similar relationship between ventricular fibrillation threshold and myocardial blood flow

With selective subendocardial ischemia produced by partial stenosis of the left anterior descending coronary artery ventricular fibrillation threshold appears to be directly related to myocardial blood flow.

can be inferred from the studies by Meesmann and colleagues<sup>13</sup> in which it could be shown that ventricular fibrillation threshold following coronary artery occlusion was directly related to collateral blood flow. Other electrophysiological parameters have also been correlated with regional myocardial blood flow. In a recent study Batsford and associates<sup>1</sup> have shown a direct relationship between effective refractory period of the ischemic myocardium and regional myocardial blood flow. The direct relationship of VFT to myocardial blood flow during subendocardial ischemia lends support to attempts to increase myocardial blood flow either by mechanical or pharmacological means during periods of prolonged ischemia where recurrent ventricular arrhythmias are often a problem.

The lack of correlation between VFT and myocardial blood flow during transmural ischemia is seen in the remote nonischemic areas of myocardium. In the left circumflex regions VFT falls significantly following left anterior descending coronary artery occlusion although flow is unaltered. One possible explanation for the decrease in VFT in remote nonischemic areas of myocardium may be that there is a delay in impulse transmission from the infarcted areas to the normal myocardium resulting in reentry. Several investigators have shown a marked delay in conduction within an area of experimental infarction.<sup>14</sup> The progressive conduction delay in the subepicardium of the ischemic region often precedes the onset of ventricular tachycardia and ventricular fibrillation.<sup>1</sup> Studies by Bloor and co-workers<sup>15</sup> showing that ventricular fibrillation threshold is related to infarct size might also tend to support this explanation since the larger the infarct the larger the area of conduction delay and hence the greater chance for reentry and ventricular fibrillation. Although this explanation is attractive it fails to account for the present finding that VFT is unaltered in remote nonischemic areas of myocardium following partial stenosis and subendocardial ischemia a situation which would also delay intraventricular conduction and favor reentry nor does it account for the finding that VFT in the subepicardial region of the left anterior descending zone was unaffected by subendocardial ischemia in the same zone.

Another possible explanation contributing to the decrease in VFT following transmural ischemia in remote areas of myocardium with

unaltered regional MBF may be the release of metabolic factors. For example catecholamines have been demonstrated to be released following experimental coronary artery occlusion<sup>16</sup> and increased sympathetic activity has been recorded from preganglionic fibers at the level of the third thoracic vertebrae. Since catecholamines are known to reduce VFT it is possible that the reduction in VFT following transmural ischemia in remote areas of myocardium with unaltered regional MBF might be due to this mechanism. Indirect support for this hypothesis comes from studies showing that propranolol may prevent reduction in VFT following experimental coronary artery occlusion.<sup>17</sup> The time course of VFT change in remote normal areas of myocardium following transmural ischemia does not appear to parallel the time course of catecholamine release in ischemia and suggests other yet unknown metabolic factors for the global electrical instability in transmural ischemia.

Support for yet unknown metabolic factors as the cause of electrical instability in ischemia comes from the study of Downar and associates.<sup>18</sup> In their study cardiac cells superfused *in vitro* with coronary venous blood draining an ischemic region developed abnormal electrophysiological properties. These abnormalities were not duplicated if the cells were superfused with coronary venous blood from a normal region even if the concentrations of potassium, lactate, oxygen and H<sup>+</sup> were equalized with those of the blood from the ischemic region.

Factors accounting for the tendency toward ventricular fibrillation in ischemia are complex and as yet poorly understood. More effective prevention in therapy of ventricular fibrillation will likely depend upon a better understanding of the interplay of all the major factors—metabolic, hemodynamic and electrophysiologic. The results of the present experiment would suggest that myocardial blood flow is but one of the major factors to be considered in our search for a better understanding of the mechanism of ventricular fibrillation.

### Summary

The role of regional myocardial blood flow on the electrical stability as determined by ventricular fibrillation threshold (VFT) was evaluated in 12 dogs during subendocardial and transmural ischemia. With selective subendocardial ischemia produced by partial stenosis of left anterior

de-ascending coronary artery (LAD) both VFT and myocardial blood flow (MBF) decreased 66.6 per cent ( $p < .001$ ) and 44.7 per cent ( $p < .001$ ) respectively from the control values in the LAD subendocardium. VFT and MBF were not significantly different from control values in LAD subepicardium and remote circumflex regions during partial stenosis of IAD.

After ligation of IAD VFT in the subepicardium and subendocardium of IAD fell 74.6 per cent ( $p < .001$ ) and 74 per cent ( $p < .001$ ), respectively from control values with an associated decrease in MBF of 98.2 per cent and 91 per cent in each of the regions. Following ligation of IAD VFT was also decreased in the circumflex subendocardium and subepicardium 62.2 per cent ( $p < .001$ ) and 79.1 per cent ( $p < .001$ ) respectively from control values while there was no change in MBF from control values in both these regions. This study demonstrates the following patterns in electrical instability with ischemia:

1. During selective subendocardial ischemia produced by partial stenosis of the LAD, VFT and MBF showed a parallel decline in the LAD subendocardial zone suggesting a direct relation up between these parameters.

2. Following LAD ligation with production of transmural ischemia the entire left ventricle became electrically unstable as measured by VFT independent of regional myocardial blood flow. This suggests that factors other than MBF significantly influence electrical instability during transmural ischemia.

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## Biatlial electrograms during coarse atrial fibrillation and flutter-fibrillation

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Atrial flutter was first determined to be a significant dysrhythmia in man by MacWilliam in 1887. It is recognized on the scalar ECG as a rapid (220 to 350 beats per minute) regular undulation of the baseline with identical broad atrial deflections (F waves). The undulation in the inferior limb leads most often resembles a sawtooth pattern. Atrial fibrillation is a form of disorganized atrial activation whose scalar ECG features consist of rapid irregular undulation of the baseline with smaller chaotic atrial deflections (f waves). In 1899, Cushman<sup>1</sup> brought atrial fibrillation to the attention of the medical world as an important rhythm disturbance in man.

Coarse atrial fibrillation (CAF) and flutter-fibrillation (FI Fib impure flutter) are disorders of atrial activation with scalar ECG features of both atrial fibrillation and atrial flutter. The ECG characteristics of CAF are those of fibrillation with superimposed larger but still irregular f waves. The scalar ECG of FI Fib generally shows the superimposition of rapid regular F waves upon a fibrillation baseline or mild variation of the amplitude and/or regularity of a flutter base-

Table 1 Cardiac diagnoses of the study population

	Number of patients
Rheumatic heart disease	12
Primary conduction system disease	9
Hypertensive heart disease	8
Arteriosclerotic heart disease	5
Congenital heart disease	3
Congestive cardiomyopathy	3
Mitral valve prolapse	3
Valvular disease (non rheumatic)	2
Others	4
Unknown	8

1 amyloid heart disease 1 pericardectomy for calcific pericarditis, 1 Wolff Parkinson White syndrome 1 Lown-Ganong-Levin syndrome

line. While the intracardiac atrial electrograms of atrial flutter and fibrillation have been described, little information is available concerning the atrial electrical events of CAF and FI Fib. Irregular high right atrial activity concurrent with regular low right and left atrial activity were noted by Puech and colleagues<sup>2</sup> in a patient with FI Fib. Zipes and DeJoseph<sup>3</sup> reported that three of ten patients with dissimilar atrial rhythms (documented by intracardiac recordings) had simultaneous scalar ECG patterns of FI Fib or CAF.

This study was designed to investigate the electrical events of the atria which occurred during the scalar ECG patterns of CAF and FI Fib.

### Methods

**Patients.** The presence of CAF and/or FI Fib on the scalar ECG was the sole criterion for

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Table II Atrial electrical activity recorded in the patient population

		No of events	Surface ECG showing	
			CAF	FI Fib
I	Biatrial fibrillation with periodic regularity	24	24	0
II	Disimilar interatrial rhythms			
	Right atrium			
	Flutter (FF > 160)	11	0	11
	Flutter (FF ≤ 160)	4	4	0
	Fibrillation	~	1	6
	Fibrillation	4	3	1
	Flutter (FF > 160)	3	0	3
	Flutter (FF ≤ 160)	1	1	0
	Fibrillation-reg	1	1	0
	Atrial tachycardia	1	0	1
III	Disimilar right intra atrial rhythms			
	High right			
	Flutter (FF > 160)	2	0	0
	Fibrillation	1	0	1
	Fibrillation	1	1	0
	Fibrillation	2	0	2
	Flutter (FF > 160)	1	0	1
	Atrial tachycardia	1	0	1
	Atrial tachycardia	1	0	1
	Low right			
	Fibrillation	1	0	1
IV	Disimilar atrial flutter rates			
	Interatrial (right = left)	4	1†	3
	Right intra atrial (high right = low right)	3	0	3
V	Fast flutter-biatrial			
	FF = 150-170 msec	12	0	12
	FF < 160 msec	4	3†	1
VI	Fragmented F deflection			
	FF > 160 msec	5	0	5
	FF ≤ 160 msec	4	2‡	2

Rhythms of high right and low right atrium were the same

†One patient demonstrated both features CAF and FI Fib

‡Both patients showed features of CAF and FI Fib

inclusion in the study. CAF was defined as fibrillation (fine undulation) of the scalar ECG base line with superimposed larger f waves ( $\geq 1$  mm) of unequal amplitude and unequal f-f intervals. ECG recordings showing a fibrillation baseline with varying periods of rapid regular waves of uniform amplitude were designated FI Fib. These dysrhythmias either occurred spontaneously or were induced by rapid atrial pacing of atrial flutter paroxysmal atrial tachycardia or sinus rhythm.

Fifty-seven patients were studied. The mean age of the patient population was 64 years (range 21 to 81) with 25 females and 32 males. Various cardiac disease states were noted (Table I) and the diagnoses were confirmed by cardiac catheterization in 30 patients. Thirty-eight (67%) of the patients had a 24-hour

cardiomegaly. 27 (47%) had clinical and/or radiologic evidence of congestive heart failure and 24 had moderate to severe chronic obstructive pulmonary disease. Right and/or left atrial enlargement was noted on cardiac fluoroscopy and/or the echocardiogram in 32 (56%) patients. Atrial conduction studies<sup>4</sup> were performed in 19 patients within one year of this study and 18 were found to have atrial conduction disease. Thirty patients were receiving a cardioactive drug at the time of study (20 patients on digitalis, five on quinidine sulfate, two on propranolol and three on propranolol and quinidine sulfate). All patients were clinically euthyroid, two of the patients were taking a thyroid preparation.

**Atrial recording studies.** Written informed consent was obtained from each patient prior to each study. No premedication was administered. In 1966

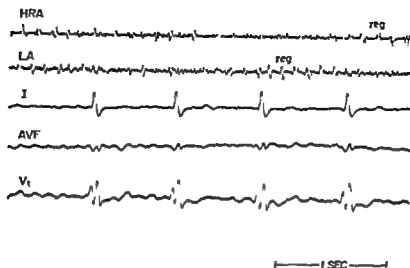


Fig 1 Electrograms from the high right atrium (HRA) and left atrium (LA) showing fibrillation with periodic slowing and regularity (reg). A similar pattern was present in the low right atrial region. Coarse atrial fibrillation was present in aVF and V<sub>1</sub>.

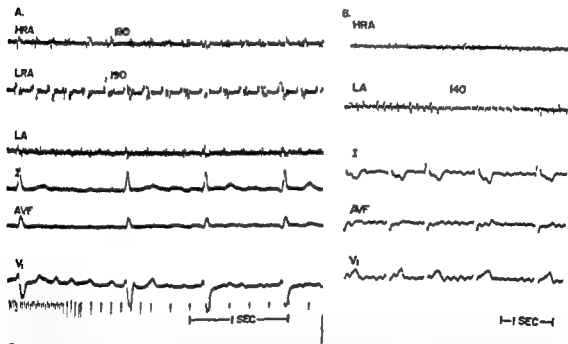


Fig 2 Biatrial electrograms during similar atrial rhythms in two patients. A High right (HRA) and low right (LRA) atrial recordings showing flutter (FF = 190 msec) and left atrial recording (LA) showing fibrillation while unipolar flutter and flutter fibrillation were noted on the scalar ECG (50 mm/sec paper speed). B Surface ECG of coarse atrial fibrillation with high right atrial (HRA) fibrillation and left atrial (LA) fast flutter (FF = 140 msec). Separate low right atrial recordings also showed fibrillation (75 mm/sec paper speed).

patients right and left atrial electrograms were recorded from bipolar electrode (interpole distance of 1 cm) catheters placed respectively within the right atrium and esophagus (posterior to the left atrium) and/or coronary sinus. A

minimum of two catheters were placed in the right atrium one for recording the high right atrial electrogram and the other for recording the low right atrial electrogram. Left atrial electrograms were not recorded in one patient. In 36

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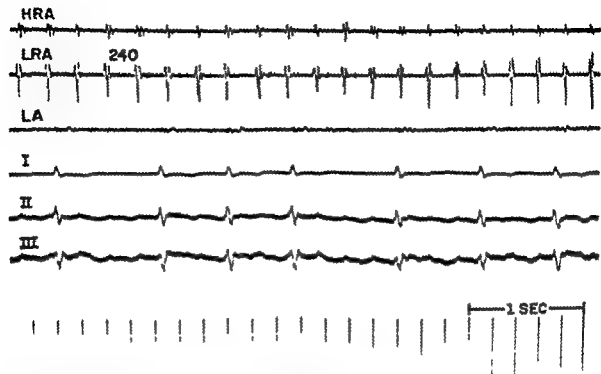


Fig 3 Right atrial flutter (HRA and LRA FF = 240 msec) and left atrial (LA) quiescence with impure flutter and flutter fibrillation pattern present on the scalar ECG

patients a six pole catheter was also placed across the tricuspid valve for the simultaneous recording of low right atrial bundle of His and the ventricular depolarizations. High right atrial (HRA) low right atrial (LRA) and left atrial (LA) electrograms and three scalar ECG leads (usually I, aV, and V) were recorded simultaneously on an Electronics for Medicine DR 12 recorder at paper speeds of 25, 50 and 100 mm/sec. Intracardiac and esophageal electrode signals were amplified at a frequency range of 30 to 500 Hz. Atrial pacing was performed with a Grass Instrument S88 stimulator and isolation unit.

An atrial electrogram showing an irregular depolarization pattern at atrial rates  $> 360$ /minute was defined as fibrillation; a regular depolarization pattern at atrial rates in the range of 220 to 400/minute was defined as flutter.

## Results

The electrical status of the atrium occurring during CAF and FI Fib in the patient population are presented in Table II.

**Fibrillation with periodic regularity.** Twenty-four of the patients had atrial electrograms showing biatrial fibrillation with periodic regularity and

regularity (Fig 1) and the scalar ECG of each of these patients revealed CAF.

**Dissimilar atrial rhythms.** Transient ( $> 1$  and  $< 5$  minute duration) or persistent ( $> 5$  minute duration) dissimilar right and left atrial rhythms were observed in 31 patients. Flutter of one atrium and fibrillation of the other was the most common form of dissimilar atrial rhythms noted (Fig 2 A and B). When the electrograms demonstrated flutter of one atrium and fibrillation of the other atrium the scalar ECG showed CAF in seven of eight patients whose flutter FF interval was  $\leq 160$  msec and showed FI Fib in 17 of 18 patients with FF intervals  $> 160$  msec. Four patients demonstrated dissimilar atrial rhythms with left atrial quiescence. Two of these patients had right atrial flutter at FF intervals of 240 and 250 msec with low amplitude flutter and FI Fib on the scalar ECG (Fig 3). Another patient had rapid right atrial flutter (FF = 160 msec) with the scalar ECG of CAF. The last patient had right atrial fibrillation (with periodic regularity) with fibrillation and infrequent coarseness on the scalar ECG. A patient previously reported had scalar ECG patterns of FI Fib and impure flutter during right atrial tachycardia and left atrial

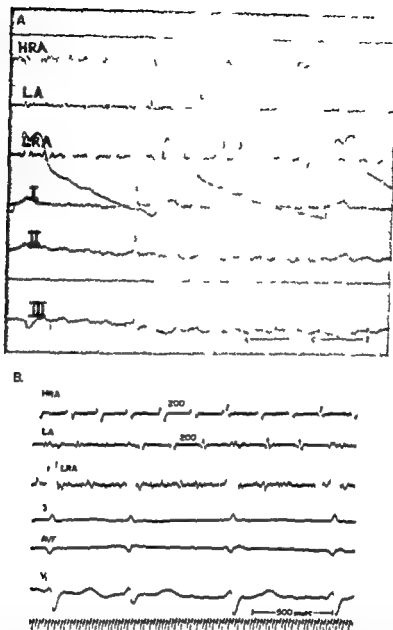


Fig 4 Dissimilar right intra atrial rhythms A High right atrium (HRA) shows fibrillation while the low right (LRA) and left atrium (LA) demonstrate flutter with an FF interval of 180 msec Flutter fibrillation was noted on the surface ECG B Another patient with low right atrial (LRA) fibrillation occurs simultaneously with high right atrial (HRA) and left atrial (LA) flutter (FF = 200 msec)

flutter and FI Fib and CAF during periods of interatrial Wenckebach

**Dissimilar right intra atrial rhythms** Dissimilar rhythms within the right atrium itself were observed in nine patients Seven instances involved flutter of either the high or low right atrium and fibrillation of the remaining portion of the right atrium (Fig 4) The simultaneous left atrial recording showed either flutter or fibril-

lation and again the scalar ECG demonstrated FI Fib if the FF interval exceeded 160 msec and CAF if the FF  $\leq$  160 msec A patient with high right atrial tachycardia (AA = 440 msec) had transient episodes of low right atrial flutter (FF = 220 msec) interchanging with periods of low right atrial fibrillation (Fig 5) No left atrial recordings were obtained on this patient and the scalar ECG showed FI Fib



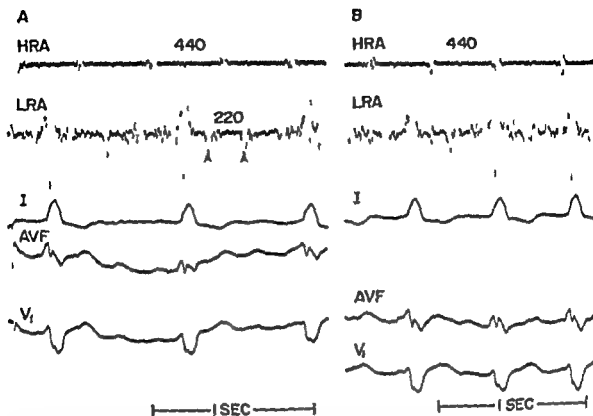


Fig 5 Two different forms of dissimilar right intra atrial rhythms in the same patient. A: High right atrial recording (HRA) showing a regular atrial tachycardia with an AA of 440 msec. A simultaneous low right atrial recording (LRA) demonstrates a regular faster atrial tachycystole (flutter FF = 290 msec). Flutter fibrillation and impure flutter pattern are present on the scalar FCG. Placement of a premature atrial depolarization (extrastimulus) in the low right atrial region changed the LRA to fibrillation as noted in panel B. The HRA remained in regular tachycardia at AA = 440/minute. Left atrial recordings are not available.

Table III Atrial electrical events noted during the scalar ECG recordings of coarse atrial fibrillation (n = 39)

Atrial electrical events		$\Delta$	n
Bistrial fibrillation with periodic regularity		21	6
Dissimilar atrial rhythms		10	2
FF > 160 msec			
RA Fib LA Fib	1		
FF < 160 msec			
RA Fib LA Fib	4		
RA Fib LA Fib	3		
RA Fib LA Fib	1		
RA Fib LA Fib	1		
Dissimilar right intra atrial rhythm		3	8
FF > 160 msec			
HRA Fib LRA Fib LA Fib	2		
FF < 160 msec			
HRA Fib LRA Fib LA Fib	1		
Fa t flutter fibrillation		2	5
FF > 160 msec	0		
FF < 160 msec	2		

Abbreviations: FF = flutter; RA = right atrium; LA = left atrium; LRA = low right atrium; HRA = high right atrium; Fib = fibrillation; FA = atrial fibrillation; qu = quiescent; RA = right atrium (high & low).

**Dissimilar atrial flutter rates** Transient unequal flutter rates of each atrium occurred in four patients. Three of these patients had scalar ECG recordings of FI Fib with right/left atrial FF intervals of 200/270, 155/170 and 230/170 msec (Fig 6). Features of both CAF and FI Fib were observed on the scalar ECG tracing of a patient with a right flutter interval of FF = 190 msec and left atrial flutter interval of 170 msec. A patient with FI Fib had transient episodes of dissimilar flutter rates within the right atrium itself: this patient had flutter (FF = 240 msec) of the left and low right atrium with a slower somewhat irregular high right atrial rhythm secondary to right intra atrial and interatrial Wenckebach (Fig 7). Another patient had two different episodes of FI Fib with unequal flutter rates within the right atrium itself: the left and high right atrial flutter was faster than the low right atrial flutter on one occasion with FF intervals of 180 and 200 msec respectively and the other episode consisted of left atrial fibrillation, high right atrial flutter with an FF interval of 200 msec and low right atrial flutter with an FF interval of 230 msec (Fig 8).

**Fast and fragmented flutter** The remainder of the patients with CAF or FI Fib had either biatrial rapid (FF  $\leq$  170 msec) flutter and/or fragmented (duration of F deflection  $\geq$  80 msec) flutter (Fig 9). In biatrial rapid flutter alone FF intervals  $\geq$  150 msec were usually manifested as FI Fib on scalar ECG and FF intervals  $<$  150 msec as CAF or CAF with episodic FI Fib.

#### Discussion

This study shows that the scalar electrocardiographic manifestations of CAF and FI Fib may be secondary to a variety of atrial electrical events. Tables III and IV summarize the atrial electrical events recorded during these dysrhythmias. Transient or persistent CAF occurred 39 times and FI Fib 53 times in this study population.

**Coarse atrial fibrillation (Table III)** The majority (62%) of CAF events were secondary to biatrial fibrillation with periodic slowing and regularization. In contrast to the regular frequency of flutter, the regularization of fibrillation showed FF intervals which were still somewhat variable and usually quite short at  $<$  140 msec (atrial rate  $>$  430/minute). The periods of regularization noted on the atrial recordings did not always

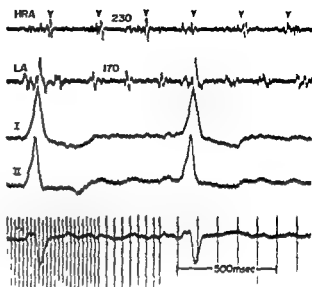


Fig 6 Transient unequal interatrial flutter rates recorded simultaneously with a flutter fibrillation pattern on the surface ECG. A lower fragmented flutter (FF = 230 msec arrows indicate measurement points of F deflections) occurred in the high right atrium (HRA) simultaneous with a faster left atrial (LA) flutter (FF = 170 msec). A very mild variation of the HRA FF interval is present. A separate recording from the low right atrium showed the same flutter rate as the HRA.

coincide with the periods of coarseness on the scalar ECG. This indicates that areas of the atria (e.g. anterior RA, lateral LA etc.) not directly recorded by the three electrodes contributed significantly to the depolarization pattern of the atria and thereby modified the scalar ECG recordings. CAF was also associated with electrograms showing dissimilar right and left atrial rhythms, dissimilar right intra atrial rhythms and fast flutter. Most of the patients (nine of 10) with CAF and dissimilar atrial rhythms had flutter rates  $\geq$  375/minute (FF  $\leq$  160 msec). Two patients with FF intervals  $>$  160 msec and the scalar ECG of CAF had dissimilar intra atrial rhythms with flutter only in the high right atrium and fibrillation in the low right and left atrium. Fragmentation of the F waves on the atrial electrograms was generally not found to be a cause of CAF, although two patients with rapid fragmented F waves (FF intervals  $<$  160 msec) had scalar features of both dysrhythmias (CAF/FI Fib, Table II). Rapid biatrial flutter alone (without dissimilar rhythms or fragmentation) was found during CAF when the flutter rate exceeded 400/minute (FF  $<$  150 msec), the pre-



Fig 7 Atrial electrograms showing regular left and low right atrial (LA LRA) flutter (FF = 240 msec) with Wenckebach periodicity occurring in the high right atrial region (HRA). The time interval (msec) between the LA and HRA deflections are indicated above the HRA recording. X = dropped HRA beat. A separate recording at 20 mm/sec. paper speed and at a slower ventricular rate showed FI Fib and impure flutter pattern on the scalar ECG.

Table IV Atrial electrical events observed during the scalar ECG recordings of flutter fibrillation (n = 53)

Atrial electrical events	No	%
Disimilar atrial rhythms	21	40
FF > 160 msec		
RA FI LA Fib	11	
RA Fib LA FI	6	
RA FI LA-quiet	2	
RA PAT LA FI	1	
FF ≤ 160 msec		
RA Fib LA FI	1	
Disimilar right intra atrial rhythm		11
FF > 160 msec		
HRA FI LRA Fib LA FI	1	
HRA Fib LRA FI LA FI	2	
HRA Fib LRA FI LA Fib	1	
HRA PAT LRA FI LA *	1	
HRA PAT LRA Fib LA	1	
Disimilar atrial flutter rates	6	11
Interatrial	3	
Right intra atrial	3	
Fast flutter-bistrial	13	25
FF = 1.0-1.00 msec	12	
FF < 1.0 msec	1	
Fragmented F deflection	7	13
FF > 160 msec	5	
FF ≤ 160 msec	2	

Abbreviations see Table III

sence of small areas of fibrillation in locations not directly recorded by the electrodes cannot be excluded in these patients

**Flutter fibrillation (Table IV)** In contrast to CAF FI Fib was never present on the scalar ECG when the electrograms demonstrated biatrial fibrillation with periodic regularity. Sixty two per cent of the FI Fib events were associated with dissimilar right and left atrial rhythms, dissimilar right intra atrial rhythms, or dissimilar flutter rates. The remainder of the FI Fib events were secondary to rapid flutter ( $FF \leq 170$ ) or fragmentation of the F waves. It appears that regular activity must be present in at least one portion of the atria in order to have FI Fib represented on the scalar ECG. The remaining portions of the atria may demonstrate fibrillation, atrial tachycardia, a different flutter rate, electrical quiescence, or a combination of these. In instances of biatrial flutter the flutter must be rapid ( $FF = 150$  to  $170$  msec) or fragmented to produce a FI Fib appearance. Ninety two per cent (37 of 40) of patients with scalar FI Fib tracings and atrial electrograms showing dissimilar rhythms or rates or fragmentation had flutter FF intervals  $\geq 160$  msec, and 92% (12 of 13) of patients with FI Fib and atrial recordings of biatrial flutter (same rates and without fragmentation) had FF intervals  $\geq 150$  msec. In general, a FF interval above 160 msec tends to produce the scalar ECG tracing of FI Fib and an interval below 150 msec will usually show CAF on ECG. In the FF interval range of 150 to 160 msec the scalar ECG pattern will depend on the atrial electrical activity occurring at the time (pure biatrial flutter = FI Fib, dissimilar rhythms or rates or fragmentation = CAF or CAF/FI Fib).

The incidence of dissimilar right and left atrial rhythms was high in our study population, occurring in 40% of the FI Fib recordings. Dissimilar right intra atrial rhythms probably belong to the dissimilar atrial rhythm family and differ only in that the boundary of the dissimilar rhythms is located between the two right atrial electrodes instead of between the right and left atrial recording electrodes. In most instances the atrial catheters were repositioned to look for variations in the atrial electrogram or to identify boundaries of flutter or fibrillation. Intermediate areas were frequently identified which showed regularity with intermittent fragmentation or irregularity and were bounded by relatively pure flutter on one border and fibrillation on another. Overdrive

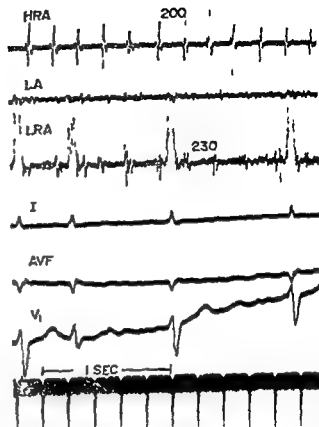


Fig 8 Transient unequal right intra atrial flutter rates in a patient with dissimilar atrial rhythms and flutter fibrillation on the surface ECG (Lead V<sub>1</sub>). The right atrium (HRA and LRA) was in flutter and the left atrium (LA) was in fibrillation. The high right atrium flutter rate was 300/minute ( $FF = 200$  msec) while that of the low right atrium was 260/minute ( $FF = 230$  msec). The FF intervals of the slower flutter (LRA) were slightly irregular ( $\leq 10$  msec variation).

pacing applied to the region of flutter (while the remainder of the atria was in fibrillation) consistently converted the flutter region to fibrillation. While these observations suggest that the dissimilar atrial rhythms of flutter and fibrillation are not independent, this study does not indicate which of the two dysrhythmias is dominant. The flutter zone may be dominant and rapid pacing of this region may move the disorganization of conduction (fibrillation zone) closer to the recording catheter. The studies of Zipes and DeJoseph suggest that the fibrillation regions are dominant and that the rhythm and rate of the flutter zone are controlled by a longer and more uniform refractory period. During overdrive pacing the refractory period of the flutter zone shortens and/or becomes non uniform, allowing more of

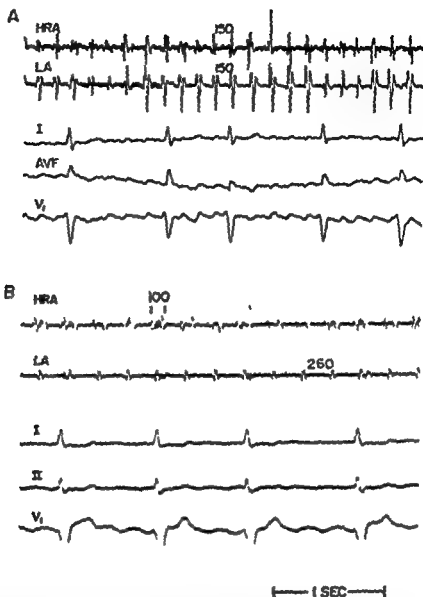


Fig 9 A Atrial recordings of fast flutter (FF = 140 msec) manifested on the scalar ECG as flutter fibrillation. B The right atrial P deflection is fragmented to a duration of 100 msec during a flutter rate of 230/minute (FF = 260 msec). The simultaneous surface ECG showed flutter fibrillation and impure flutter.

the fibrillatory impulses to enter the region. Overdrive pacing of right atrial flutter during left atrial quiescence did not alter the flutter rhythm and rate or converted the region into fibrillation. Although the electrical quiescence was explored with multiple catheter locations (full length esophageal and coronary sinus readings) at high gain and various recording frequencies it is possible that very fine fibrillation was present in or around the quiescent region.

The mechanism of different intra- or interatrial flutter rates (dissimilar atrial flutter rates) is not clear. The region with a slower flutter rate probably has a longer refractory period and is depen-

dent upon conduction from the faster flutter region for its impulses. The activation of a passive region with a longer refractory period to the more rapid regular impulses of another region would be slightly irregular as noted in Figs 6 and 8 or would show a set conduction pattern as observed in the patient with interatrial and right intra-atrial Wenckebach (Fig 7) and in another patient with interatrial Wenckebach and 2:1 interatrial conduction.<sup>8</sup> The dissimilar atrial flutter rate events were all transient ( $\leq 5$  minutes duration) implying that this rhythm disturbance is unstable and will probably not persist as a chronic atrial dysrhythmia.

Most patients in this series had cardiac disease with cardiomegaly alone (20%) or cardiomegaly with clinical and/or roentgenographic congestive heart failure (47%). Fluoroscopic and/or echocardiographic data revealed that atrial enlargement was present in 56% of the patients. Twenty-five of 29 (86%) patients who spontaneously developed CAF or FI Fib had cardiomegaly and/or atrial enlargement and/or evidence of congestive heart failure. Thus, only four of 29 patients (14%) with spontaneous CAF or FI Fib did not have cardiomegaly, atrial enlargement, or congestive heart failure. Two of these remaining four patients underwent atrial conduction time measurements, both demonstrated prolonged atrial conduction times indicative of atrial conduction disease. Therefore, of 29 patients who had developed spontaneous FI Fib or CAF, a cardiac pathophysiologic etiology was not identified in only two patients. The patient prototype for CAF and FI Fib in our study was an individual with a form of cardiac disease accompanied by one or more of the following: (1) cardiomegaly, (2) atrial enlargement, (3) congestive heart failure, or (4) atrial conduction disease.

This study does not provide direct information on the mechanisms of atrial fibrillation or flutter, but it does illustrate some of the interactions of the two dysrhythmias. The scalar ECG recordings of the relatively common dysrhythmias, CAF and FI Fib, appear to be secondary to an interesting spectrum of atrial electrical events.

### Summary

Right and left atrial electrograms were recorded in 57 patients who demonstrated coarse atrial

fibrillation or flutter-fibrillation on the scalar electrocardiogram. Atrial electrograms in coarse atrial fibrillation most often showed biatrial fibrillation with periodic slowing and regularity, while dissimilar interatrial or right intra-atrial rhythms were noted less frequently. Flutter-fibrillation on the scalar ECG required the presence of rapid regular tachycardia (flutter) somewhere in the atria and was usually associated with dissimilar interatrial or right intra-atrial rhythms, dissimilar atrial flutter rates, or fast or fragmented flutter. Coarse atrial fibrillation and flutter-fibrillation may be secondary to a variety of atrial electrical events.

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# Extension of experimental infarction with nicotine and estimates of infarct size

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There has been a great deal of interest in both the public and the scientific quarter in the past three decades in the possible role that certain constituents of tobacco smoke play in the development of coronary atherosclerotic heart disease (CAHD) and its sequel myocardial infarction and in the occurrence of sudden death.<sup>1</sup> This study is focused upon one constituent of tobacco smoke nicotine and is designed to address the question whether or not the acute administration of nicotine after infarction alters infarct size.

A secondary purpose of this study was to further test in a larger group of animals with an intervention an electrical infarct sizing technique previously reported.

## Methods

Twelve dogs selected to weigh between 20 and 30 kilograms were anesthetized with sodium pentobarbital intravenously administered 30 mg per kg. Controlled respiration was established with a Harvard pump respirator utilizing room air. Tidal volumes were calculated to consider the size of the animal and the dead space of the instrumentation. Prior to any intervention normal arterial blood gas values were verified.

From 142 surface sites potentials were recorded on analog magnetic tape which was subjected to analog to digital conversion and digitized at a sampling rate of 1 000 per second. For digitization for averaging 100 cycles and for time alignment of the averaged data the fiducial mark was obtained from a shaped and filtered simultaneous control Lead II. The effective frequency response of the entire system was between 0.2 and 3 000 Hertz. Onset of activation was specified with the help of a PDP 9 computer search of the 142 leads in which the first of eight successive increases in the root mean square value of the total surface electrocardiogram was programmatically determined. The information is displayed in isometric projection map form at 1 msec intervals throughout the period of ventricular excitation. Such data were obtained and recorded both prior to and one week after closed chest myocardial infarction. A point by point subtraction of the chest voltages recorded after infarction from those recorded before was performed msec by msec from each recording site (Fig 1). The root mean square value of the difference map was compared at each msec and represented the electrical estimate of infarct size. This estimate of size was compared with the anatomic estimate of infarct size described below.

The technique of infarction utilized a Sones No 7 or 7½ catheter advanced under fluoroscopic control via the right carotid artery and positioned well into the left main coronary artery at the bifurcation of the circumflex and the left anterior descending branch. After a left coronary arteriogram was performed a 0.025 inch catheter guide wire was passed and positioned in the left anterior

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Fig 1 High frequency recordings of surface potential have been obtained at each grid intersection of the body surface maps. Left extremes of the map represent the center of the back the eleventh vertical grid line from the left represents the midsternal line. The superior map border is at a level just below the clavicle while the inferior map border is at the level of the umbilicus. The animal's thorax is portrayed as a 30 degree isometric projection map in order that positive voltage expressions appear as peaks and negative ones as sinks. A point by point subtraction of the map recorded after myocardial infarction from the map recorded before myocardial infarction is carried out at each grid intersection at 1 msec intervals throughout the QRS complex. A difference map is thus calculated at each msec interval and its volume is determined. Such volumes representative of infarcted muscle are correlated with the actual anatomic volume at each msec (See text)

descending branch distal to the origin of the first diagonal (Fig 2). The catheter was removed and a sterilized metal bead was placed over the guide. The catheter was then again inserted over the guide and the bead was advanced to the proper position in the left anterior descending branch.

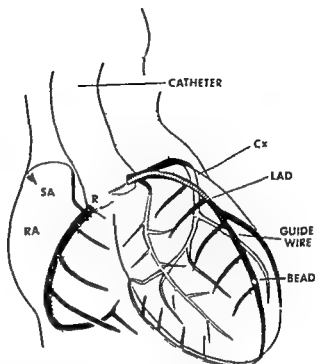


Fig 2 The technique of myocardial infarction utilizing a completely closed-chest preparation is demonstrated. Through an arteriotomy in the right carotid artery a coronary arteriogram is performed with an end hole catheter. The guidewire is inserted through the catheter into the approximate location for bead placement. The catheter is removed, a metallic bead is placed over the guide, the catheter is replaced and the bead is expelled off the end of the guide at the desired location.

After placement the location of the bead was further verified with a follow up coronary arteriogram. Constant recording of multiple lead surface voltages allowed immediate confirmation of the current of injury.

The catheter instilled bead technique of producing a controlled size myocardial infarction was developed over the course of five years. A stable survival rate of 76% was achieved. Our ability to control infarct size was tested in ten animals divided into two groups. The first group was sequentially infarcted in one set of experiments and compared with the second set who were infarcted 10 months later utilizing the identical technique but in a different laboratory setting entirely. Paired *t* and Student's *t* tests revealed no differences in the infarct size (determined morphologically as described below), reassuring us that we had achieved a technique that was reproducible. Animal weight predicts heart



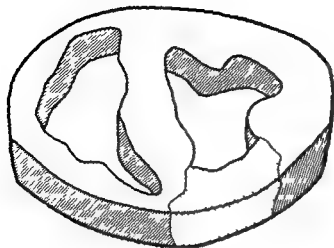


Fig 3 A diagrammatic representation of the method of preparing the hearts in 1 cm. slices for staining and planimetry or photograph followed by planimetry. The planimeterized area of infarction was obtained for each 1 cm. slice and its percentage of the total myocardium was calculated (See text)

size in normal dog quite well. Thus by continuing care in selection of animal size very homogeneous groups resulted which were comprised of dogs whose weights and heart masses were not significantly different at the outset.

An infusion of nicotine in the amount of 800  $\mu\text{g}/\text{minute}$  was initiated after a stable electrical state had been reached following lead placement. The infusion was continued for a 15 minute period after which the animals were observed until electrical stability was again achieved. The dogs were then returned to the animal care facility to recover from anesthesia.

One week after infarction a second total body surface map was recorded following which the dogs were rapidly killed. The intact hearts were removed and in the first six animals the hearts were immediately frozen with liquid nitrogen then sliced and prepared for histochemical staining. Each measured centimeter slice of myocardium was subsectioned for microscopic study using 40 micron thick sections. Stains were applied for hematoxylin and eosin as well as periodic acid Schiff staining and special histochemical stains for lactic and succinic dehydrogenase.

From these six dogs heart preparations it was ascertained that at one week the extent of the infarcted zone could be clearly determined for reproducible planimetry without the necessity of special dye staining. Twelve 1 cm. thick slices of the myocardium were photographed and traced onto ruled paper so that the

total surface area for each slice could be determined. The planimeterized area of the myocardial infarction was obtained for each slice and its percentage of the volume of the total myocardium was calculated from the area estimates by Newton's method<sup>10</sup> (Fig 3). The percentage of infarction then was calculated and expressed as the percentage of the total heart volume rather than the left ventricular volume alone.

Infarction size could then be expressed in terms of the amount estimated electrically, and the amount determined by direct morphologic assay. Further the degree of correspondence of the two methods of sizing was established by determining the correlation between the anatomically determined infarct volume and each instantaneous estimate of the electrical loss.

## Results

After initiation of nicotine there was an increase in sinus node discharge up to 40% of the baseline rate for a period of about five minutes. During this same period single ventricular premature beats, salvos and short bursts of ventricular tachycardia occurred. During the last 10 minutes of exposure the animals exhibited relative electrical stability with total cessation of sequential ventricular premature beats and a complete absence of ectopic activity or only rare single ventricular premature beats. At the time of return to the animal facility some 90 minutes post infarction the two groups were indistinguishable in terms of rhythm and conduction.

In order to apply a paired *t* test to groups of the same size to compare the sizes of the infarctions in terms of percentage of heart volume we eliminated one of the 10 dogs not having received nicotine. In order not to prejudice the comparison in favor of the hypothesis that nicotine given acutely increases infarct size we excluded from consideration for the paired *t* test only the dog from the group not exposed to nicotine with the smallest percentage of infarcted myocardium. Total heart volumes ranged from 69.41 to 123.3 cubic centimeters with no difference between groups. Infarctions ranged from .99 cubic centimeters (which was in the non infarct group and not included in the paired *t* test) to 13.4 cubic centimeters.

The volume of infarcted myocardium expressed as percentage of total heart volume was deter-

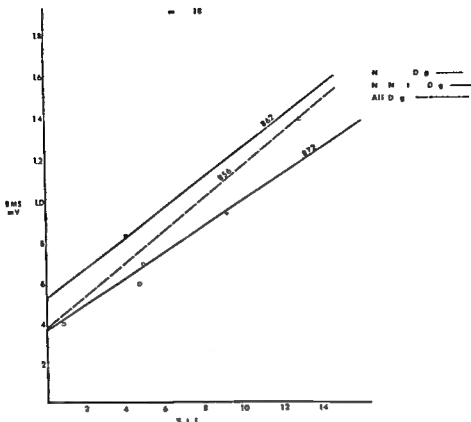


Fig 4 At msec 18 the root mean square (RMS) in mV of the infarct map is compared with the morphologically determined size of infarction. Regression lines demonstrating the level of correlation between the electrically determined infarct volume and the morphologically determined infarct volume for three groups of animals are shown. The first regression line (dashed line) demonstrates the correlation coefficient of the total group of animals, the dotted line represents the correlation coefficient for the animals subjected to nicotine, and the solid line represents the animals not exposed to nicotine. Note the high degree of correspondence between the electrical and the morphologic infarct volumes. Maximum correlation in each animal occurred during the middle of ventricular activation at 17 or 18 msec.

mined to be greater in the nine animals of the nicotine group compared to the nine animals not exposed to nicotine who had the largest infarctions ( $p < 0.0001$ ).

In Fig 4 we see regression lines demonstrating the level of correlation between the electrical and morphologic zones of infarction in all 19 dogs (dashed lines) in the dogs exposed to nicotine (dotted lines) and in the dogs not exposed to nicotine (solid line).

In Fig 5 we see the results of viewing the degree of correlation between the anatomic infarct volume and the electrical infarct volume at each millisecond throughout ventricular activation. In both the dogs exposed to nicotine and those who were not, correlation between anatomic and electrical infarction size was maximal in mid ventricular activation. For instance, a correlation coefficient of 0.88 was established at 17 msec after the

onset of activation in those dogs not exposed to nicotine, and at 18 msec the best correlation coefficient of 0.86 was achieved in the nicotine exposed dogs. Further, the reproducibility of the electrical and morphologic techniques is supported by the similarity in the degree of correlation between the electrical infarct size and the anatomic infarct size when all dogs are considered as a group, when those exposed to nicotine are considered alone, and when those not exposed to nicotine were considered alone.

## Discussion

The increase in infarct size as the result of nicotine exposure is probably multifactorial and is certainly complex. One consideration is the observation of the increased heart rate and ventricular arrhythmias confined to the first few minutes. Recently, a relationship between ven-

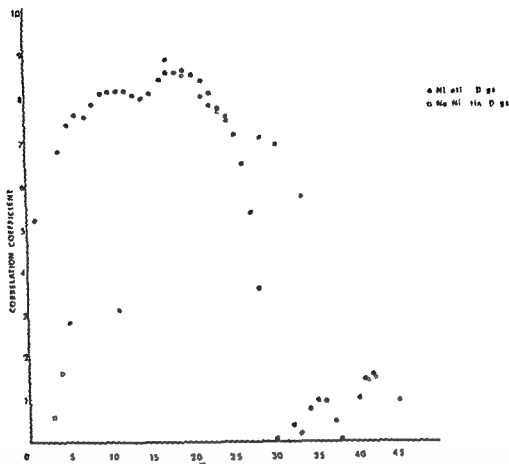


Fig. 5 The degree of correlation between the anatomic infarct volume and the electrical infarct volume at each millisecond throughout ventricular activation is demonstrated. The closed circles represent the dogs exposed to nicotine and the open squares show the degree of correlation for the dogs not subjected to nicotine. Note the rising correlation in both groups from onset of activation. Best correlation occurred at msec 16, 17 and 18 in both groups with deterioration toward the end of activation.

ventricular arrhythmias and infarct size has been emphasized. Certainly during the immediate early phase of nicotine administration the ventricular arrhythmias in the nicotine group were quite prominent whereas ventricular ectopy occurring immediately after coronary occlusion had virtually disappeared in the group not exposed to nicotine. By 90 minutes post infarction however the groups were indistinguishable as far as ventricular ectopy was concerned. Therefore the period of difference in the incidence of ventricular arrhythmias was confined to the initial period of nicotine administration.

The effect of absolute size and the location of infarction as a predictor of arrhythmias is a consideration. It should be pointed out that these were relatively small infarctions. The occlusions were not of the proximal left coronary artery which frequently produces ventricular fibrillation rather they were more distally located and

consistently at relatively the same site. We were not, then confronted with either acute ventricular fibrillation and the subsequent need to defibrillate electrically nor were we confronted with the early mortality often associated with acute infarction during the first four hours.<sup>11</sup> Neither did our animals experience the sequels of extensive infarction resulting in a low cardiac output state<sup>12,13</sup> with their consequent increase in endogenous catecholamines and the propensity for both ventricular arrhythmias and tachycardia related increase in infarct size.

We believe therefore that the extension of the infarct size with a single nicotine intervention probably is primarily the result of the dominant sympathomimetic pharmacologic response to the drug. Nicotine has a paradoxical effect in that depending on dose and route of administration it can result in slowing of the sinus node discharge as well. This was not observed in this series of

experiments The sinus tachycardia can be explained in part by discharge of epinephrine from the adrenal medulla resulting in an accelerated rate Additionally studies have demonstrated nicotine to result in the release of catecholamines from isolated organ preparations The sympathomimetic response to nicotine is contributed to further by the activation of chemoreceptors in the aortic and carotid bodies resulting in reflex vasoconstriction increased arterial blood pressure and tachycardia \* Downey and colleagues<sup>1</sup> in a study of regional myocardial blood flow during nicotine infusion report that coronary vasodilation occurred in normal myocardium but in ischemic myocardium it increased only in proportion to aortic pressure This along with their observation in the presence of beta blockade of nicotine producing a further drop in cardiac output and rate and the abolition of previously present ventricular arrhythmias emphasizes the presence of nicotine's sympathetic effect<sup>21</sup>

Mean left atrial pressure rose much more markedly in animals rendered ischemic with left anterior descending artery ligation than in non ischemic controls Further aortic flow decreased by 12% This likely represents the increased impact of the peripheral sympathetic response on an already dysfunctional left ventricle

It is difficult to relate in either a supporting or a conflicting fashion the results of Downey and associates flow studies to our work Although nicotine increased flow in their ischemic model initially the transmural gradient across the myocardium was unchanged The flow increase seemed to be merely a function of an acute rise in aortic pressure While there was no evidence of shunting away from the ischemic zone certainly with aortic flow down and LV function compromised the increased flow state could be anticipated to be transitory

While the amount of nicotine administered 800 µg/minute is a large dose it is not an overwhelming dose considering the fact that some cigars today contain from 15 to more than 40 mg of nicotine and the acutely fatal adult dose is about 60 mg

It has been demonstrated that smokers who inhale may absorb up to 90% of the nicotine in the mainstream smoke drawn into their mouths<sup>2</sup> Further it has been demonstrated in cats and man that very comparable arterial levels of nicot-

ine result from either inhaled or intravenously administered nicotine<sup>3</sup> The appropriateness of the model is further supported by work suggesting a predictable relationship between blood levels of nicotine and nicotine content in inhaled smoke

In addition to showing the increase in infarct size as a result of nicotine exposure this work offers further confirmation of the validity of using the difference map approach in estimating infarct size The consistency of finding in this series of 19 as in our earlier series of 10 that the best instant of correlation of electrical infarct volume with morphologic volume is between 16 and 18 msec is exciting We believe that this time during the course of ventricular activation is just prior to the time of the maximal wavefront reaching the epicardial surface When any technique of electrical subtraction is utilized one is actually attempting to specify the dimension of the zone of infarction Subtracting voltages occurring after infarction from control or baseline potentials results in the removal of all wavefronts outside the infarct zone Thus a subtrahend of infarction voltages is left The nearer this difference surface potential or infarction potential corresponds to the difference internal wavefront the better the correlation should be between the actual infarct extent and the difference potential By concentrating on mid activation and by restricting the method to instances without acquired major conduction defect one avoids the error introduced by loss of the basic endocardial to epicardial activation sequence Such loss would render comparisons invalid in left bundle branch block for instance and would render them valid only during early activation in right bundle branch block

In conclusion then this study had a twofold purpose First we wished to explore the effect of acute limited short term exposure to nicotine on the size of myocardial infarction We have demonstrated that nicotine acutely administered results in a significantly larger volume of infarcted muscle when all other variables are constrained as nearly as possible Secondly we set out to confirm whether the utility of infarct sizing employing body surface potential difference maps continued to demonstrate its good performance previously reported when a pharmacologic intervention had been imposed and a larger number of animals were considered We conclude that infarct size electrically determined

from the body surface difference map demonstrates a high correlation with the morphologically delineated infarct volume whether or not a pharmacologic intervention has been imposed. The technique may prove useful in the assay of drug intervention as well as in surgical techniques employed in the modification of infarct size.

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## Atrial reentry in chronic repetitive supraventricular tachycardia

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Repetitive supraventricular tachycardia is a special arrhythmia characterized by shorter or longer runs of tachycardia separated by one or more sinus beats.<sup>1-4</sup> It has generally been believed to reflect either reentrant mechanisms or rapid firing of ectopic foci. In repetitive supraventricular tachycardia, atrioventricular nodal reentry and reentry involving an accessory atrioventricular pathway have been demonstrated. In this report a case of chronic repetitive supraventricular tachycardia is presented with reentry located within the atria.

### Case report

Electrophysiologic study of a 78-year-old woman was performed because of frequent episodes of tachycardia since 1967. After written consent of the patient was obtained, His bundle electrocardiography and programmed atrial and ventricular stimulation procedures were carried out by approved techniques.

Onset of the tachycardia. ECGs during palpitation showed the pattern of repetitive supraventricular tachycardia. Bouts of tachycardia were usually interrupted by four to eight sinus beats with P-R intervals of 0.16 second and narrow QRS complexes (Fig 1). The tachycardia always started after gradual shortening of the sinus cycles at a critical P-P interval of about 600 to 640 msec. A-H intervals of sinus beats provoking a run of tachycardia and of the preceding sinus beats were the same, indicating that A-H prolongation was no prerequisite to start a tachycardia (Fig 1). While spontaneous reappearance of the tachycardia was usually preceded by at least four sinus beats, an atrial extrastimulus with an A-A

interval equal to or shorter than the critical P-P interval could always induce the tachycardia, even after the first sinus beat (Fig 2). Ventricular extrastimuli during sinus rhythm could neither provoke the tachycardia nor capture the atria. The morphology of P waves during tachycardia differed from that during sinus rhythm, but it was not of retrograde contour. High right atrial electrograms preceded low atrial electrograms (Fig 3), excluding the possibility of retrograde atrial depolarization.

Termination of the tachycardia. The tachycardia was terminated by a spontaneous atrial extrasystole (Fig 4). Programmed atrial extrastimulation was performed to delineate the range of coupling intervals of atrial extrastimuli suppressing the tachycardia. Atrial extrastimuli with A-St intervals of 240 msec or longer could not, and those with 220 msec or shorter coupling times could always terminate the tachycardia (Fig 5). In this figure it can also be noted that extrastimuli with longer coupling times are accompanied by wide QRS complexes, while the extrastimulus with the shortest coupling time is not, indicating a gap phenomenon in the left bundle branch conduction. Progressive shortening of A-A intervals of extrastimuli not suppressing the tachycardia resulted in progressive lengthening of the return atrial cycle A-A, as shown in Fig 6.

### Discussion

Mechanisms of repetitive supraventricular tachycardias can be delineated in clinical electrophysiology. Tachycardias of ectopic origin show the following features: (1) Early extrastimuli inserted during the tachycardia may enter the ectopic focus and reset its timing, causing a pause less than compensatory. (2) The tachycardia cannot be initiated and terminated by critically timed extrastimuli. In the described case these criteria for diagnosis of ectopic tachycardia were absent.

The tachycardia in our patient was initiated and terminated by critically timed atrial extra-

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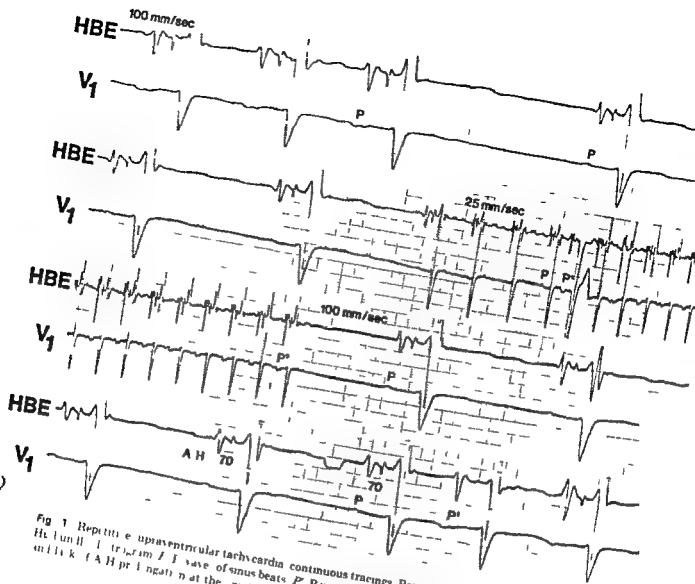


Fig 1 Repetitive upventricular tachycardia continuous tracings. Paper speed 100 and 25 mm/second. HBE Holter II I tracing. P wave of sinus beats. P' P waves of tachycardia. Note the differing P and P' contours with the A-H prolongation at the onset of the tachycardia in the bottom strip.

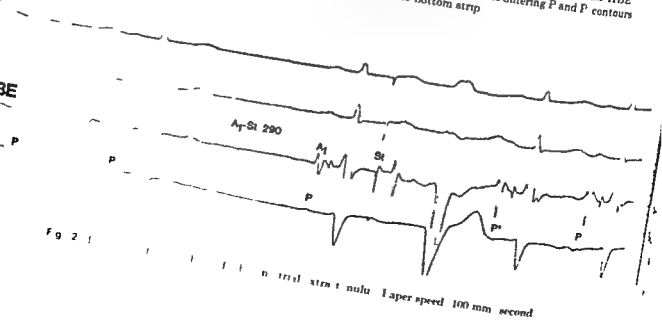
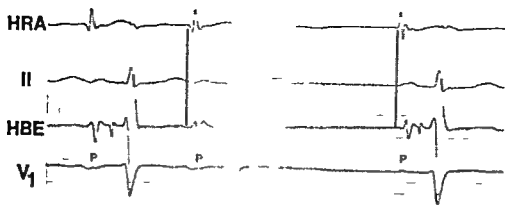


Fig 2 Atrial fibrillation. Paper speed 100 mm/second.



**Fig 3** Antegrade atrial activation sequence 4  
electrogram Paper speed 100 mm/second

br and tachycardia HRA High right atrial

stimuli suggesting a reentrant mechanism. Lack of A-H prolongation preceding the tachycardia does not favor and the antegrade atrial activation sequence during tachycardia preclude an atrioventricular nodal reentry. The relatively long R-P interval during tachycardia and inability of ventricular extrastimuli to capture the atria are against utilization of an accessory pathway for retrograde conduction to the atria.

Diagnostic criteria of atrial and sinus nodal reentry are identical apart from differences in P and A wave morphology and in atrial activation sequence. In sinus node reentry the contours of P and A waves and the atrial activation sequence are identical with those during sinus rhythm. P and A waves in atrial reentrance should be different from sinus P and A waves and atrial activation depending on the site of the atrial reentry may be variable. In our case the changes in P and A wave morphology during supraventricular tachycardia favor atrial reentry.

Atrial reentry in repetitive supraventricular tachycardia—to our knowledge—has not been described so far.

## Summary

Atrial reentrance as a mechanism of the tachycardia was demonstrated in a 28 year old patient suffering from chronic repetitive supraventricular tachycardia. Criteria for diagnosis included the following (1) Repetitive supraventricular tachycardia.

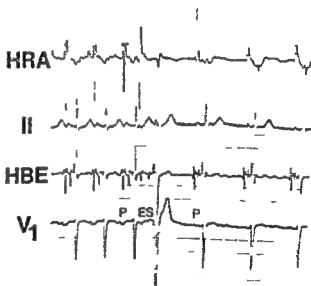


Fig 4 Termination of the tachycardia by a spontaneous atrial extrasystole ES Paper speed 25 mm./second

cardia was induced and terminated by properly timed atrial extrastimuli (2) Return cycles of all atrial extrastimuli not abolishing the tachycardia were fully compensatory (3) A H prolongation was not a prerequisite to induce the tachycardia (4) The contours of P and A waves during tachycardia differed from those in sinus rhythm but atrial activation remained antegrade (5) A concealed anomalous pathway could not be proved



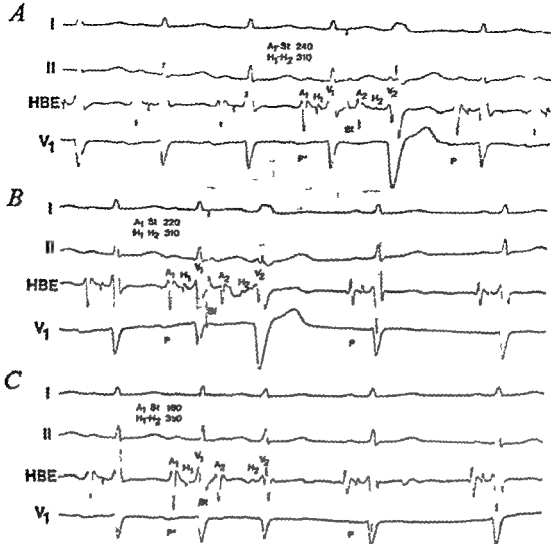
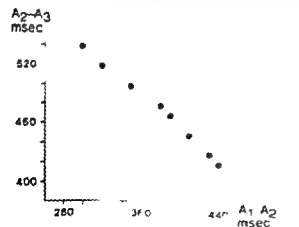


Fig 5 Termination of the tachycardia by critically timed atrial extrastimuli. Paper speed 100 mm/second. An atrial extrastimulus with A-St interval of 240 msec (A) did not and those with A-St intervals of 220 msec or shorter (B and C) did terminate the tachycardia. Note that the A-St interval of 180 msec was accompanied by an H-H interval of 300 msec (C) followed by a narrow QRS complex (C) in contrast to extrastimuli with longer coupling times (A and B) which resulted in a left bundle branch block QRS (gap in left bundle branch).



6 Return atrial cycles during tachycardia

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# Congenital atresia of the left coronary ostium and hypoplasia of the left main coronary artery

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Anomalies of the coronary arteries are not common comprising less than 46 per cent of congenital malformations of the heart.<sup>1</sup> The case to be reported is a rare congenital malformation of the coronary arteries atresia of the left coronary ostium with hypoplasia of the left main coronary artery. A single coronary system results which is not a true anatomical single coronary artery. In addition the clinical and angiographic findings may be confused with anomalous origin of the left coronary artery from the pulmonary artery.

## Case report

A six month old female infant was admitted to the Pediatric Unit of Crouse-Ingers Memorial Hospital with a two-day history of progressive respiratory distress. Prior to this illness the patient had been completely asymptomatic with normal growth and development. Birth and family history were unremarkable. The infant appeared acutely ill and on physical examination was mottled gray with shallow respirations, pulse 180, respiratory rate 80, blood pressure faintly audible at 100/60. Examination of the head and neck was unremarkable. The lungs revealed crackles; no rales were heard. The heart was enlarged to percussion; the heart tones were of poor quality with a gallop rhythm at the apex. A faint ejection systolic murmur was heard at the left sternal border. There was hepatomegaly 3 cm below the right costal margin. All peripheral pulses were diminished.

The pertinent laboratory findings revealed an elevated white blood count of 18,000 with a slightly left shift. The

arterial blood gases were pH 7.35, PCO<sub>2</sub> 38, PO<sub>2</sub> 9 and arterial saturation of 79 per cent. The cardiac enzymes 12 hours after admission revealed a CPH of 9,630, SGOT of 88 and an LDH of 996.

The electrocardiogram taken on admission (Fig. 1) demonstrated the pattern seen in anterior lateral wall myocardial infarction. There was inversion and marked ST segment depression in Lead I and in the left precordial leads. A deep Q was present in Lead aV<sub>1</sub>.

The x-ray examination (Fig. 2) revealed marked cardiomegaly and the vascular pattern was consistent with pulmonary venous congestion.

The patient was digitalized, placed in oxygen and cardiac catheterization was performed on the first hospital day (Table 1). The data were consistent with poor myocardial performance. There was no evidence of left to right shunting. The right atrial and pulmonary artery pressures were moderately elevated. There was a marked elevation of left atrial pressure and left ventricular end diastolic pressure.

Angiograms were interpreted as consistent with the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery. The left atrial angiogram (Fig. 3) revealed dilated left atrial and left ventricular chambers. There was akinesis of the anterior and lateral walls as well as the apex of the left ventricle. An aortic root angiogram (Fig. 4) showed filling of a large right coronary artery arising from the anterior aortic cusp. There was delayed opacification of a small, delicate left main coronary artery via collaterals from the right coronary artery. The anterior descending and circumflex arteries both filled from the collaterals. The high posterior position of the reconstituted main left coronary artery was consistent with the location encountered with anomalous origin of the left coronary from the posterior wall of the pulmonary artery. However the main pulmonary artery did not opacify on the aortic root injection and a pulmonary artery arteriogram did not demonstrate filling of a coronary vessel.

Open heart surgery was performed. The left coronary artery did not arise from the pulmonary artery as expected. There was atresia of the left coronary ostium and marked hypoplasia of the left main coronary artery. The left circumflex artery appeared normal. The left anterior descending artery was extremely small and would not accept a graft. An attempt was

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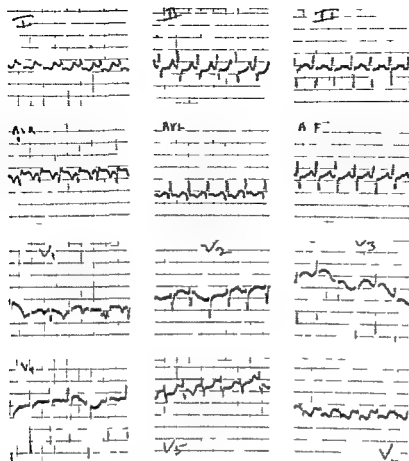


Fig 1 Electrocardiogram demonstrating an anterior lateral wall myocardial infarction



Fig 2 X ray on admission demonstrating cardiomegaly and pulmonary venous congestion



Fig 3 Frontal film of left atrial angiogram with the left ventricle in end systole. There is anterior apical and anterior septal akinesis.



Fig 4 A and B The frontal (A) and lateral (B) aortic root angiogram demonstrates normal origin of a large left main coronary artery. There are septal collaterals from the right to left coronary artery. Observe the reconstituted anterior descending circumflex and main left coronary artery. Sequential films showed delayed filling via collaterals. Note high posterior position of main left coronary artery.

Table 1 Cardiac catheterization data

Site	Pressure mm Hg systolic/ diastolic	Flow ml/min	O <sub>2</sub> saturation (%)
Superior vena cava	—	—	56
Right atrium	12/6	10	50
Right ventricle	40/20	—	48
Main pulmonary artery	46/13	30	43
Left atrium	31/19	21	87
Left ventricle	84/76	—	87
Aorta	85/41	20	94 (on O <sub>2</sub> )

modest dilatation of the left main coronary ostium. The patient did not undergo surgery.

At autopsy the heart was markedly enlarged. The right coronary artery appeared normal. The left circumflex artery was normal arising from the aortic left main coronary. The left anterior descending branch was small measuring 1 mm. The left coronary ostium was dilated 3 mm with difficulty. There was a large left ventricular myocardial infarction involving the apex, lateral wall and posterior part of the ventricular septum. The myocardium of the left main coronary artery revealed a filling defect in the left main coronary artery resected a few centimeters from the aorta on the wall adjacent to the myocardium.

## Discussion

Non patency of the left coronary ostium associated with atresia of the proximal left main

coronary has been infrequently described in the literature as an isolated finding. Only recently has it been included in a classification of primary congenital anomalies of the coronary arteries. It has been reported in association with other congenital malformations of the heart and in some systemic diseases. It is absent from most reviews of coronary artery occlusive disease and myocardial infarction in infancy and childhood including Stricker's frequently quoted review, which outlines eight categories of occlusive coronary disease. No description of atresia of the left main coronary artery and ostium specifically appears in his discussion. More recent discussions of occlusive congenital coronary artery disease and myocardial infarction in infants and children also contain no mention of the lesion. A case very similar to the patient presented is reported in a textbook discussion by Lurie and represents the first inclusion of this lesion in a formal categorization of congenital anomalies of the coronary arteries producing occlusion and myocardial infarction. Levin and associates, in the most recent series of cases of congenital coronary artery disease also formally document and separately classifies this entity.

In addition to the above two cases there have been five case reports in the literature which fit

the description of the case of Lurie<sup>1</sup> and our own case Mullins and co workers<sup>1</sup> describe a case in a ten year old male who underwent successful aortocoronary bypass grafting. The case of Fortuin and Roberts<sup>11</sup> in a 60 year old male who was diagnosed at autopsy following sudden death attests to the fact that the lesion spans a wide age range and has unpredictable morbidity and mortality. MacMahon and Dickinson<sup>1</sup> describe the case of a six week old with myocardial infarction who at autopsy revealed non patency of the right coronary ostium and stenosis of the proximal segments of both the right and left coronaries. The case of Goormaghtigh and colleagues<sup>1</sup> in a nine year old female was discussed in the context of an unproven infectious process and labeled as idiopathic. The autopsy findings demonstrated non patency of the left coronary ostium associated with atresia of the first 1 cm of the left main coronary artery and stenosis of the right coronary ostium. This case is similar to ours and we believe represents a primary congenital anomaly of coronary arteries. There has been confusion in the literature in the distinction between the entities of congenital atresia of the coronary ostium and proximal coronary arteries and true single coronary artery. This is typified by the report of Murphy<sup>1</sup> entitled 'Single Coronary Artery'. He describes a 71 year old male in whom the pathologic findings are actually identical to the cases of atresia of the left coronary ostium and hypoplasia of the proximal portion of the left coronary artery described above.

The paper by Fortuin and Roberts<sup>1</sup> considers the possibility that atresia of the coronary ostium and hypoplasia of the proximal coronary artery segment may be one of the causes of true single coronary artery. However reviews<sup>1</sup> of the subject of congenital single coronary artery in man contain no cases where an atretic proximal coronary artery was found. Some of the cases described did have dimples at the site of the absent coronary ostium. Embryologically it is suggested that single coronary arteries arise by failure of development or displacement of one coronary anlage. The developmental defect in congenital atresia of the coronary ostia and hypoplasia of the proximal main coronary artery segments may be similar to that producing true single coronary artery but the resultant malformations are anatomically and clinically distinctly different.

Cardiac angiography should be a useful diag-

nostic tool to delineate the lesion in this report. However both our case and the case described by Lurie<sup>1</sup> were diagnosed preoperatively as anomalous origin of the left coronary artery from the pulmonary artery. The criteria by cardiac catheterization for the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery has been outlined and include retrograde filling of the left coronary artery through collaterals with opacification of the pulmonary artery on aortic root injection, the presence of a negative jet in systole or forward flow in diastole into the anomalous left coronary on pulmonary root injection, and left to right shunting by oximetry at the main pulmonary artery level. The absence of these findings in a suspected case of anomalous origin of the left coronary artery from the pulmonary artery should suggest the possibility of the lesion under discussion. But it should be recognized that anomalous origin of the left coronary artery from the pulmonary artery with poor collateral flow may not meet these criteria. Additionally the presence of a short left main coronary artery filling retrograde and ending blindly should be diagnostic of congenital atresia of the ostium and hypoplasia of the left main coronary. Differentiating between the two conditions is of surgical importance but may not be possible clinically or angiographically.

In summary the entity of congenital atresia of the coronary ostium and proximal left main coronary artery should be added to formal classification of primary congenital lesions of coronary arteries which cause occlusive coronary disease and/or myocardial infarction in infancy and childhood. As an isolated event the lesion can be unilateral or bilateral and probably represents a failure of development of the coronary artery anlage. Pathologically it has been confused with congenital single coronary artery and clinically it can mimic anomalous origin of the coronary artery from the pulmonary artery. Absence of the usual catheterization and angiographic findings for anomalous origin of the left coronary from the pulmonary artery should raise the diagnostic possibility of congenital atresia of the coronary ostium and hypoplasia of the proximal main left coronary artery.

## Summary

The clinical and pathological findings are described in a six month old female with unusual congenital malformation atresia of



Fig 4 A and B The frontal (A) and lateral (B) aortic root angiogram demonstrates normal origin of a large right coronary artery. There are septal collaterals from the right to left coronary artery. Observe the reconstituted anterior descending circumflex and main left coronary artery. Sequential films showed delayed filling via collaterals. Note high posterior position of main left coronary artery.

Table 1 Cardiac catheterization data

Site	Pressure mm Hg systolic/ diastolic	m = mean	O saturation (%)
Superior vena cava	—	—	76
Right atrium	12/6	10	72
Right ventricle	40/20	—	48
Main pulmonary artery	40/13	30	43
Left atrium	31/19	21	87
Left ventricle	84/5	—	87
Aorta	110/41	72	94 (on O <sub>2</sub> )

made at dilatation of the left coronary ostium. The patient did not survive the surgery.

At autopsy the heart was markedly enlarged. The right coronary artery appeared normal. The left circumflex artery was normal, arising from the left main coronary artery. The left anterior descending branch was small, measuring 1 mm. The left coronary ostium situated just below the left ventricular septum. There was a large left ventricular aneurysm arising from the proximal left ventricular septum. The main left coronary artery revealed a focal stenosis on the wall adjacent to the aneurysm.

## Discussion

Non-patency of the left coronary ostium associated with atresia of the proximal left main

coronary has been infrequently described in the literature as an isolated finding. Only recently has it been included in a classification of primary congenital anomalies<sup>1</sup> of the coronary arteries. It has been reported in association with other congenital malformations of the heart and in some systemic diseases. It is absent from most reviews of coronary artery occlusive disease and myocardial infarction in infancy and childhood, including Stryker's frequently quoted review which outlines eight categories of occlusive coronary disease. No description of atresia of the left main coronary artery and ostium specifically appears in his discussion. More recent discussions<sup>2,3</sup> of occlusive congenital coronary artery disease and myocardial infarction in infants and children also contain no mention of this lesion. A case very similar to the patient presented is reported in a textbook discussion by Iurii<sup>4</sup> and represents the first inclusion of this lesion in a formal categorization of congenital anomalies of the coronary arteries producing occlusion and myocardial infarction. Levin and associates<sup>5</sup> in the most recent series of cases of congenital coronary artery disease also formally documents and separately classifies this entity.

In addition to the above two cases, there have been five case reports in the literature which f

## Heparin and atherosclerosis A review of old and recent findings

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Atherosclerotic disease and its complications are the leading cause of death in most advanced nations. The medical profession therefore logically is interested in the prevention of atherosclerosis and the amelioration of this modern epidemic. The current debate as to the relative merits of medical versus surgical therapy to retard the progress of established coronary disease attests to this interest. There is considerable experimental and clinical evidence, older and more recent, which indicates that heparin would be useful in the prophylaxis and therapy of atherosclerosis. Since this evidence is rarely discussed, a valuable additional modality for clinical atherosclerotic disease may be overlooked.

For several decades following discovery of the naturally occurring anticoagulant named heparin,<sup>1</sup> investigators only concerned themselves with its chemical nature, extraction from animal tissues, and its use as an anticoagulant. Interest in heparin in relation to atherosclerosis dates from the accidental observation in 1943 that heparin abolished post-alimentary lipemia in dogs *in vivo*. This did not occur when heparin was added to lipemic blood *in vitro*, indicating the essential role of a tissue factor in the process. These findings were soon confirmed in other animals and in man. It was then shown that pre-heparin lipemic plasma was cleared *in vitro* by the addition of plasma withdrawn after the injection of heparin *in vivo*, establishing the presence of a lipemia-clearing factor in the blood produced by heparin injection. Ultracentrifugal methods revealed that an injection of heparin in rabbits and man was followed by a rapid disappearance of

the larger triglyceride-rich lipoproteins from the plasma,<sup>2</sup> a loss of neutral fat from the blood,<sup>3</sup> an absolute increase in alpha or high-density lipoproteins,<sup>4</sup> and a shift in cholesterol from the beta to the alpha lipoproteins.<sup>5</sup>

The mechanism underlying these significant lipid changes became more clear when it was found that the post-heparin lipemia-clearing factor caused the lipolysis of triglycerides into free fatty acids and glycerol.<sup>6</sup> The role of serum albumin as the carrier molecule for the free fatty acids was recognized.<sup>7-9</sup> The active lipolytic substance was then extracted from rat heart and since it was active upon triglyceride-rich lipoprotein substrates rather than upon simple triglycerides, the enzyme was named lipoprotein lipase.<sup>10</sup> At the same time a lipemia-clearing factor was found in some human plasmas without the prior injection of heparin.<sup>11</sup> This plasma factor was then shown to be lipolytic in nature and its identity with post-heparin lipoprotein lipase and its distinction from pancreatic lipase was established. The demonstration of the active lipolytic enzyme in tissues and blood without the prior injection of heparin proved that it was a normal physiologic substance, a point previously in question.

Subsequent work has shown that several other lipolytic enzymes appear in the blood after heparin injection. However, lipoprotein lipase is the major one, and the results of many investigations have established that lipoprotein lipase enzymatic activity is the major physiologic pathway for the removal of triglycerides from the blood stream. This applies to alimentary triglycerides transported in the blood as chylomicrons and to hepatically synthesized triglycerides transported as very low-density lipoproteins. It is generally

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accepted that the bulk of circulating triglycerides is hydrolyzed at the capillary endothelium. However, some circulating endogenous lipolytic activity has been found in the majority of normal individuals when platelet rich plasma was tested<sup>1</sup>. In a few people this plasma lipolytic activity is substantial<sup>1</sup>.

Although a highly purified lipoprotein lipase obtained from rat post heparin plasma and apparently essentially free of heparin, effects the hydrolysis of lipoprotein triglycerides, much evidence indicates that endogenous heparin normally plays a role in the lipoprotein lipase mechanism. Lipoprotein lipase is inhibited by heparin binding agents<sup>2,3</sup>. Bacterial heparinase reduces the activity of chicken adipose tissue lipoprotein lipase. The intravenous injection of a potent heparin antagonist in man resulted in a rise of fasting serum triglycerides<sup>4</sup>. Circulating heparin binding immunoglobulins are associated with markedly increased serum triglyceride levels. Lipoprotein lipase is released from its tissue sites but is loosely bound to heparin. The bond is probably ionic and reversible<sup>5</sup>. Heparin also stabilizes the activity of the enzyme<sup>6</sup> and binds it to its substrate, the triglyceride rich lipoprotein, the negatively charged groups of heparin probably complexing with the positively charged amino groups of the lipoprotein<sup>7</sup>.

The role of heparin in facilitating the hydrolysis of lipoprotein triglycerides via lipoprotein lipase bears much resemblance to its function in catalyzing the reaction between antithrombin III and plasma coagulant proteins.

This brief summary of the probable role of endogenous heparin activity in the removal of triglyceride from the blood was necessary since defects in or interference with this physiologic pathway are important in the genesis of hypertriglyceridemia and those hypercholesterolemic states which are secondary to it. There is evidence that such defects and interferences do exist.

An earlier monograph<sup>8</sup> presented the results of numerous investigations which using fat tolerance tests showed that there is a delay in the removal of ingested fat from the blood in atherosclerotic patients thus contributing to the increased serum lipids found in these individuals. One of the factors that could play a role in such delay would be an inadequate amount of circulating endogenous heparin. The normal presence of chemically defined heparin in the blood stream in

man has never been proven. It has been shown in rat blood<sup>9</sup>. However, an extract has been obtained from normal human plasma which has the biologic activity of heparin. In 1947<sup>10</sup> 53 milligrams of such material was isolated from 5 liters of human plasma using the standard method of extraction of heparin from animal tissues. In 1954 an anticoagulant heparin like substance was isolated from small quantities of human plasma<sup>11</sup> and the next year increased yields were obtained<sup>12</sup>. The material had the same biologic activity as commercial heparin. It had anticoagulant activity in sheep plasma and enhanced antithrombotic cofactor activity and its anticoagulant activity was neutralized by protamine. Furthermore, the plasma extract was strongly metachromatic with toluidine blue after prolonged dialysis and moved identically with commercial heparin on electrophoresis using toluidine blue paper. It inhibited the generation of intrinsic plasma thromboplastin<sup>13</sup>. It is possible that the extract contained other mucopolysaccharides besides heparin. However, the one closest to heparin is heparan sulfate and it has only about ten per cent of the anticoagulant potency of heparin. Also recent x-ray fiber diffraction studies have shown that approximately 20 per cent of the heparan sulfate molecule is identical to heparin. It is probable that the heparin like activity of heparan resides in its heparin moiety. Thus, from the standpoint of physiologic function it matters little whether the extract obtained from normal human plasma is heparin or heparan or both. Nor does it matter that heparin may not be a homogeneous substance. What is important is that biologic heparin activity normally is present in human plasma.

Quantitation of the anticoagulant activity in the plasma extract from clinically normal individuals showed that plasma heparin activity varied from 1 to 24 units per ml or from 1 to 24 mg heparin per liter of plasma, a value very close to that obtained in 1947<sup>10</sup>. This level of heparin activity though low is physiologically significant since only 0.1 unit of heparin in 0.8 ml of normal human plasma markedly accelerates the inhibition of activated factor X by antithrombin. More relevant is the finding of an inverse relationship between endogenous plasma heparin activity and the triglyceride bearing very low density (SF12-400) serum lipoproteins. The results were statistically highly significant but

the relatively low correlation coefficient indicated that other factors in addition to the level of plasma heparin activity affected the lipoprotein levels. It is unfortunate that these findings have not been investigated by others using reliable methods for the determination of circulating endogenous heparin activity since they are both physiologically and clinically significant. They suggest that hypertriglyceridemia with its associated hypercholesterolemia and enhanced atherogenesis may result in part from a deficiency of circulating heparin activity analogous to the insulin deficiency present in some diabetic subjects. Studies of mast cells in experimental animals have also led to the suggestion that a high susceptibility to atherosclerosis might be related to a deficiency of endogenous heparin.<sup>1</sup>

Studies of circulating and tissue lipoprotein lipase activity have also given evidence of a relation of this normal enzymatic pathway to hypertriglyceridemia. The triglyceride bearing very low density lipoproteins (Sf12-400) were statistically significantly lower in individuals who had demonstrable endogenous plasma lipemia clearing activity. Lower lipoprotein lipase activity associated with the beta lipoproteins was found in patients with essential hyperlipidemia. Adipose tissue lipoprotein lipase activity was inversely related to the level of serum triglycerides.<sup>1</sup> Subjects with hypertriglyceridemia have lower values of heparin released lipoprotein lipase activity.<sup>2</sup> Various types of abnormalities have been reported which interfere with efficient operation of the heparin lipoprotein lipase mechanism and result in increased serum triglycerides. Chylomicra and larger lipoproteins resistant to the action of lipoprotein lipase have been described. Absence of post heparin lipolytic activity was reported. A qualitative defect in post heparin lipoprotein lipase was found in three siblings with hyperchylomicronemia.

There have also been articles describing circulating inhibitors of heparin and lipoprotein lipase in atherosclerotic patients with increased lipids. Some apoproteins interfere with the activation of lipoprotein lipase and a highly purified glycoprotein inhibitor of postheparin lipoprotein lipase and bovine milk lipoprotein lipase has been described. Earlier studies had shown that thrombin extracts of white blood cells and platelets and human tissue extracts inhibited

lipolysis to some extent. Circulating clotting factors and lipoproteins compete for heparin. The addition of lipoproteins to a mixture of heparin and serum prevented the activation of antithrombin.<sup>3,4</sup> Thus an increased concentration of certain lipoproteins can cause hypercoagulability. Conversely if coagulation factors are increased there might be inadequate heparin activity available to properly activate the lipoprotein lipase mechanism and hypertriglyceridemia would result. The subject obviously requires much further investigation.

Now we can discuss how injected heparin may act to retard the atherosclerotic process. To begin with if a relative inadequacy of or interference with heparin activity are factors in many subjects with increased serum triglyceride levels supplying additional exogenous heparin is logical. It is analogous to the use of insulin in diabetes, corticosteroids in adrenal insufficiency or thyroid extract in hypothyroidism. Apart from that many of the known actions of heparin would be beneficial in retarding the atherosclerotic process and its complications. These actions of heparin can logically be divided into two categories.

#### 1 Effects at the vascular endothelial surface

#### 2 General effects within the circulating blood

In some areas the two broad categories overlap. Of course in relation to the atherosclerotic process ultimately all effects are on the arterial wall itself. Let us therefore first consider actions of heparin at the vascular endothelium.

Earlier work had suggested that injected heparin had an affinity for endothelium. Uptake of heparin at the endothelial cell junctions was shown by various investigators.<sup>5,6</sup> Tissue culture studies using human and animal endothelial cells showed that metachromatic heparin granules localized on the cell membrane surface. Recently this important point has been confirmed. Heparin was recovered from the endothelium in rats after its injection by the intravenous intraperitoneal or subcutaneous routes.<sup>7</sup> There was a much greater concentration of heparin on the endothelium than in the blood. When the aortic or venous endothelium of dogs, rabbits or rats was exposed to dilute heparin solutions there was a very effective uptake of heparin by the endothelium. This took place even when the contact with heparin was less than one minute and the endothelial heparin was much more concentrated than

the heparin in the surrounding medium. Heparin was not removed after endothelial fixation by 10 to 20 washings with Locke's solution. It is not known how long this fixation of heparin at the endothelium persists, but it is apparently for much longer than anticoagulant activity can be demonstrated in the blood. When exogenous heparin is taken up by mouse peritoneal macrophages, the heparin-containing granules are present for about three weeks. Recent studies using radioactively labelled heparin also showed that heparin has a high binding affinity for human endothelial cells even when excessive amounts of other glycosaminoglycans were present. This binding affinity corresponded to about 10 heparin molecules per endothelial cell. Other findings suggested that the heparin was bound to the surface of the endothelial cells and was not extensively degraded since it retained the ability to bind to antithrombin III. The authors pointed out that endothelial heparin would anchor antithrombin and so increase antithrombotic activity at that site.

Injected heparin localized and concentrated on the endothelial surface has many beneficial actions. In the first place it may simply reinforce the physiologic functions of endogenous heparin activity at the normal vascular wall. There are heparin-containing mast cells immediately beneath the endothelium of most blood vessels so that heparin is easily available at that site. Metachromatic staining characteristic of heparin and heparin-like substances is present on the vascular intimal surface of animals and man. Antithrombotic and antithrombolytic generating activity has been demonstrated in this metachromatic material of the vascular endothelium. Heparin was identified electrophoretically in the glucose-aminoglycans isolated from the intima plus media of human aortic tissue. Endothelial cells in tissue culture secrete mucopolysaccharides related to heparin, the bulk of which is heparan. Since heparan contains a heparin moiety, heparin activity is normally present at the endothelial surface. At this site there is evidence that it functions in the repair of injured vascular endothelium. Normal intima has a negative electric potential which becomes positive after injury. After heparin injection there is a marked increase in the net negativity of the vascular intima, apparently as a result of the absorption of heparin at the surface of the

injured endothelium. There is an inverse correlation between the negative charge at the vascular interface and vascular injury in vivo.

Exogenous heparin concentrated on the endothelial surface would act to prevent endothelial injury. It is accepted that the atherosclerotic process is enhanced and perhaps initiated at the sites of endothelial injury. The intact endothelium is a permeability barrier partially protecting the artery against atherogenic serum factors. When it is damaged, one of the earliest endothelial reactions is contraction of the endothelial cells with consequent widening of the gaps between the cells and increased permeability to plasma atherogenic factors. At the same time there is an increased sticking of platelets to the injured endothelial surface, predisposing to thrombosis. Heparin binds and inactivates many of the agents that injure endothelium. Among these are histamine, serotonin, lysozyme, angiotensin, bradykinin, some components of complement, some viruses, and many toxins. Virus infections induce atherosclerosis in experimental animals and the disease resembles human atherosclerosis. Immunologic injury accelerates atherosclerosis, especially when some degree of hyperlipidemia is present, and heparin modifies a variety of allergic reactions. Heparin minimizes platelet adhesion to damaged vascular endothelium, and to artificial shunts. Aggregated platelets release various materials which may harm the vascular wall, such as epinephrine, serotonin, lysosomal enzymes, and cationic proteins. Human platelets contain an enzyme capable of degrading a major part of the heparan normally associated with the endothelial cell surface. This degradation was inhibited by heparin even though heparin itself is degraded by the enzyme. A platelet factor also stimulates the proliferation of arterial smooth muscle cells which are key cells in atherogenesis. Thus platelet adhesion to endothelium may enhance the atherosclerotic process by injuring endothelium in various ways and by stimulating smooth muscle cell proliferation apart from the role of platelets in the initiation of arterial thrombi. Injected heparin concentrated on the endothelial surface would minimize platelet adhesion and these harmful platelet effects.

Apart from the protection against endothelial injury and platelet adhesion, endothelial exogenous heparin has a direct potent local anti-

thrombic action. Injured endothelial cells and the exposed subendothelial tissue may initiate coagulation. The intima and media of human aorta have high thromboplastic activity, as does human atheroma material. Thus any intimal injury could release thromboplastic substances which could give rise to thrombin formation upon contact with the coagulation factors normally present on the vascular intima.

It is also probable that irreversible platelet aggregation and the platelet release reaction which probably initiate arterial thrombi are dependent on the generation of thrombin from the coagulation factors in the plasma surrounding the platelet surface. Thrombin itself produces endothelial injury, is a potent mitogenic agent, and increases platelet adhesion to the vessel wall.

An anti-thrombin agent (hirudin) markedly decreased the adherence of thrombin aggregated platelets to endothelial and smooth muscle cells. Platelets adhere to endothelial cells in culture after they have been treated with thrombin or activated factor X. Minute quantities of heparin prevent the activation of factor X. Endothelial heparin therefore would minimize thrombin formation and its effects at sites of endothelial injury. Heparin also markedly inhibited the intimal smooth muscle cell proliferation that resulted from vascular injury.

Heparin was more effective than platelet inhibiting drugs in preventing thrombus formation in experimentally injured carotid arteries.

Another action of exogenous heparin at the endothelial surface should be mentioned. Minute amounts of heparin in the medium inhibited the uptake of serum lipids by human and animal arterial endothelial cells in tissue culture. Unfortunately, this has not been investigated by other workers. This effect, which would act to decrease the entrance of atherogenic serum lipoproteins into the vascular intima cells, probably results from the negative charge of heparin localized on the cell surface.

Let us now discuss the general effects of injected heparin in the circulation which might be important in relation to atherogenesis. We will first start with the effects upon blood lipids. As mentioned earlier in this article, the clearing of lipemia after heparin injection reflects a rapid disappearance of chylomicrons and very low density lipoproteins from the plasma resulting from the lipolysis of their triglyceride content, a

decrease in circulating triglycerides and an absolute increase in alpha or high density lipoproteins. In general, after a 20,000 unit injection of heparin subcutaneously, it takes about 48 hours for the lipid values to revert to their initial levels if a normal diet is ingested. These changes in the circulating lipids have several important effects.

To begin with the reduction in the average level of circulating atherogenic lipoproteins results in a decreased insudation of these lipoproteins into the arterial wall, although the magnitude of this response is hard to quantitate. Decreased infiltration of atherogenic lipoproteins not only would slow the atherosclerotic process but might allow mechanisms of repair or regression to operate more efficiently. Increased lipemia adversely affects the regeneration of injured arterial endothelial cells, and can also produce primary endothelial injury.

Lipemia also has harmful effects within the blood itself which would be decreased when lipid levels are lower. Increased agglutination of erythrocytes with resultant capillary stasis has been observed after high fat meals. The infusion of fat emulsions accelerated coagulation as shown by thrombin generation tests, an action completely prevented by small doses of heparin. Fats increased the resistance of blood clots to lysis. This increased thrombotic tendency with increased lipemia may result from the effect on platelets. The latter are then more sensitive to thrombin induced and to ADP induced aggregation. Both saturated and unsaturated fats increase platelet adhesiveness in man with saturated fats doing so to a greater extent. The action of fats on platelet adhesiveness is greater in patients with coronary disease than in healthy individuals. The correction of hyperlipidemia in patients with coronary heart disease increased their previously decreased platelet survival times.

Another harmful effect of increased serum lipids is that upon tissue oxygen supply. This important subject, which has relevance both to atherogenesis and to tissue and myocardial function, has been largely ignored. Before discussing it further, it is necessary briefly to consider how the oxygen demand of the arterial wall is met.

Oxygen is supplied to the arterial wall from the arterial lumen and from the vasa vasorum which nourish the outer two thirds of the vessel wall. The intima and inner media are entirely depen-

dent on the diffusion of oxygen from the lumen. In larger mammals and man the avascular wall thickness of large arteries is approximately 1 mm close to the limiting distance over which oxygen diffusion will adequately supply tissue needs'. Oxygen tension is lowest in the media with a sharp rise in the tissue just below normal endothelium. Thus the media and its smooth muscle cells are constantly on the brink of hypoxia and are sensitive to alterations in oxygen tension. In man due to intimal thickening the distance over which oxygen must diffuse to reach the media increases with age. In addition early fatty lesions of atherosclerosis markedly interfere with oxygen diffusion through the intima. These anatomic and physiologic considerations implicate the oxygen economy of the arterial wall in the pathogenesis of atherosclerosis. Beyond this there is much evidence that hypoxia accelerates the atherosclerotic process'.

Does lipemia affect tissue oxygenation? The uptake of oxygen by the red blood cells of hypercholesterolemic rabbits was decreased. Studies of forearm arteriovenous oxygen differences' and then of total oxygen consumption' in atherosclerotic patients showed an increase of tissue oxygen consumption after heparin from initial subnormal values almost up to normal. The increase in oxygen consumption did not occur at a time when clotting was most prolonged by heparin but coincided with maximal lipid clearing. Oxygen inhalation, oral anticoagulants and saline placebo had no such effect on oxygen consumption. More recent studies using an ear oximeter showed an increase in the rate of oxygen transfer from blood to tissue after heparin in subjects with coronary atherosclerotic disease. On the other hand intravenous fat emulsions slightly decrease arterial oxygen saturation in man and in experimental animals. There is a decrease in skin oxygen tension in man coincident with postprandial lipemia with a rapid rise to normal levels after heparin. In the non lipemic state heparin had no such effect. Post alimentary lipemia prevented the usual enhancement of myocardial oxygen extraction after exercise. These various studies indicate that lipemia impedes oxygen diffusion.

There is evidence that suggests how this occurs. Layers of fat particles at cell surfaces may react with other substances and these reactions are altered by the degree of lipid in the mole-

cules'. " Due to their property of combining with oxygen fats affect estimates of the solubility or diffusion constants of oxygen". The diffusion of oxygen through the blood plasma is also decreased by an increased concentration of plasma proteins and lipoproteins even over normal physiologic ranges'. " Other possible mechanisms whereby abnormal concentrations of lipoproteins may affect oxygen utilization have been discussed elsewhere". Whatever the mechanism the decrease in lipemia after heparin injection increases tissue oxygen supply.

A relative and absolute reduction in the alpha or high density lipoproteins in patients with known coronary atherosclerotic disease was found long ago' but its significance was overlooked until the past few years. Several epidemiologic studies recently summarized provide good evidence that higher levels of high density lipoproteins are an independent protective factor against the development of atherosclerosis and contribute to increased longevity'. A mention earlier when heparin is injected one of the lipid changes is an absolute increase in the alpha or high density lipoprotein fraction. Chemical analysis confirmed that a higher percentage of the total cholesterol was in the alpha lipoprotein fraction after heparin. It was noted' that the redistribution of lipids elicited by heparin injection was toward the pattern present in normal subjects without known atherosclerotic disease. A current investigation is substantiating these results (unpublished data). In the majority of patients with coronary atherosclerosis high density lipoprotein levels or the percentage of the total cholesterol in the high density fraction are temporarily increased following a single injection of heparin. This may well be another significant pathway whereby exogenous heparin is beneficial. Unfortunately there are no studies of the effect of long term administration of heparin on HDL levels.

Another channel by which exogenous heparin may act in relation to atherogenesis is by displacement of the major site of lipoprotein lipase action. Normally the bulk of chylomicrons and very low density lipoprotein triglyceride hydrolysis probably occurs at the capillary surface. The removal of triglyceride from the large lipid laden particles leaves cholesterol rich remnants and beta lipoprotein in high concentration at and within the endothelium. Rat aorta needed

smooth muscle cells showed an enhanced uptake of these remnant particles.<sup>11</sup> Thus it has been proposed that atherogenesis is linked to the normal interaction of endothelial lipoprotein lipase with triglyceride rich lipoproteins. Injected heparin displaces much of the enzyme into the plasma. A greater portion of triglyceride lipolysis then takes place within the circulating blood leaving a lower concentration of the cholesterol rich remnant particles at the endothelial surface available for endothelial cell uptake.

For many years there have been reports suggestive of an enhanced tendency to coagulation in atherosclerotic individuals. Clinicians have long been aware that some patients required much more heparin than usual to achieve therapeutic anticoagulation. Documentation of a hypercoagulable state has been difficult but has received support from more recent studies. Heparin resistance has been reported resulting from abnormal plasma globulins.<sup>12</sup> Decreased

antithrombin III and increased serum heparin neutralizing activity were found in survivors of myocardial infarcts.<sup>13</sup> Increased platelet factor 4 levels in the blood were present in patients with thromboembolic states and in patients with severe coronary heart disease. Increased heparin neutralizing activity (platelet factor 4) is present in and released from aggregated platelets of men with established coronary heart disease.

There is much slower disaggregation of such platelets probably resulting from the facilitation of thrombin generation when more heparin neutralizing factor is released. Low rates of platelet disaggregation also occur with greater frequency in patients with peripheral arterial disease.<sup>14</sup> Patients whose platelets disaggregate slowly may be more likely to develop a thrombus when platelets contact exposed subendothelial connective tissue. As noted earlier lipoproteins interfere with the activation of antithrombin III by heparin. Small doses of heparin injected twice a week corrected the increased coagulability and platelet adhesiveness found in some patients with atherosclerotic disease. Estrogens decrease the activated factor X inhibitory activity of plasma without changing the level of antithrombin III and so produce a hypercoagulable state which is completely reversed by trace amounts of heparin.

Heparin neutralizes many of the cationic proteins released by platelets, leukocytes, and other sources. These proteins influence blood

coagulation and fibrin precipitation and so have potential significance in intravascular coagulation. The neutralization of a hypercoagulable tendency in the blood if present is another way in which injected heparin would benefit atherosclerosis particularly if microthrombi are involved in atherogenesis.

As stated earlier in this article endothelial injury probably is the initial prerequisite to the sequence of events leading to atherosclerotic lesion. The mechanisms leading to endothelial injury are not clear. It has been proposed that activated serum complement is a key factor involved in endothelial injury. The complement system is an effector pathway of the inflammatory response which normally is present in an inactive form in the bloodstream. It is activated specifically by infections and immune complexes or non-specifically as by aggregation of macromolecules. Circulating immune complexes have been found in a substantial fraction of patients with vascular disease and their effect in activating complement may be a major pathway whereby immunologic injury accelerates atherosclerosis.

The consequences of complement activation include increased vascular permeability, attraction to leukocytes, adherence of complement coated complexes to formed elements of the blood, and alterations in cell membranes that can lead to lysis and cell death. Recently it was shown that inhibition of the third component of complement by cobra venom decreased the extent of myocardial necrosis after coronary occlusion in experimental animals illustrating the important role that complement can play in the inflammatory response even when activated non-specifically.

Activation of the complement system results in the sequential interaction of the serum proteins or components of which it is composed. Since the complement system is potentially capable of producing drastic effects it has safeguards to control its activation. These include various inhibitors. It has long been known that heparin interfered with the action of complement. Early studies identified several possible sites of this inhibitory action by heparin ranging from classical early to late component functions. Recent studies confirm this. Normal serum has a protein called C1 esterase inhibitor which inhibits the activated first component of complement. Heparin at very low concentrations greatly poten-

tiates the activity of this inhibitor and the authors noted that the kinetics of the effect were strikingly similar to those of the action of heparin plus antithrombin in the coagulation sequence.<sup>11</sup> Complement activation involves amplification of the third component of complement via the formation of an amplification convertase. Both commercial and native rat mast cell heparin inhibit the generation of this amplification convertase<sup>12</sup> which may well determine whether the initial activation of the complement sequence by the classical or by the alternative pathway eventuates in the effective utilization of the terminal components.<sup>13</sup> The classic pathway of complement activation is progressively inhibited by increasing concentrations of heparin whereas its effect in the alternative pathway is apparently more complex.<sup>14</sup> Since complement activation involves a cascade of protein interactions<sup>15</sup> similar to the coagulation cascade since heparin in minute amounts immediately markedly potentiates the activity of a serum inhibitor of complement activation<sup>16</sup> it may not be too far afield to suggest that injected heparin perhaps reinforces a physiologic activity of endogenous plasma heparin. In any event if the activation of complement is an important pathway of endothelial injury, injected heparin would at least partially inhibit it and so limit tissue damage.

These various effects of heparin at the endothelium and in the bloodstream indicate that it would be valuable in the prophylaxis of atherosclerosis. What results have been obtained? In cholesterol fed animals the majority of investigators reported a substantial reduction in the extent of experimental atherosclerosis as compared to controls.<sup>17</sup> Heparin also arrested the further development of pre-established aortic atheroma despite continued cholesterol fat feeding.<sup>18</sup> It retarded experimental atherosclerosis in endarterectomized iliac arteries. Heparin sulfate (heparin) which has heparin like activity also decreased the degree of experimental atherosclerosis.<sup>19</sup> Negative results with heparin in retarding atherosclerosis in experimental animals also have been reported.<sup>20</sup>

It is possible that the extreme hypercholesterolemia attained in experimental animals and species and strain differences contributed to some of the negative findings.

Prophylactically in human with established coronary atherosclerotic disease, heparin has been given subcutaneously. From this the hepa-

rin is slowly released into the blood thus providing low but persistent levels of circulating heparin which also give continued higher heparin concentrations at the endothelial surface. Most investigations of the use of long term heparin therapy in human subjects with prior acute myocardial infarction(s) have shown good results. Four of these were controlled studies. In the first<sup>21</sup> in which 20 000 units of concentrated aqueous heparin were injected subcutaneously twice a week over a two year period there were four cardiovascular deaths in 103 patients on heparin as compared to 21 deaths in 117 patients who received placebo injections. The two groups of patients were comparable, and the difference in the annual mortality rate (2.4 per cent vs 11.5 per cent) was statistically definitely significant,  $p = .01$ . The next study compared full anticoagulant doses of heparin given twice daily with oral anticoagulant therapy over a two year period.<sup>22</sup> The mortality rate in the heparin group (53 patients) was 5.6 per cent as compared to 10.7 per cent in the 51 patients on prothrombin depressing drugs. In the third study,<sup>23</sup> 46 male patients received heparin 20 000 units twice a week and 43 men were given placebo injections for a six year period. Over that time there were seven acute myocardial infarcts and one death in the heparin group and 10 infarcts and six deaths in the placebo group. The difference in deaths was statistically significant. In the fourth controlled but smaller investigation, heparin was given in daily doses of 5 000 to 10 000 units subcutaneously<sup>24</sup> and compared to oral anticoagulants. Over a 3.3 year period there was one cardiac death in the 30 patients in the heparin group (1 per cent annual mortality rate) as compared to 10 cardiac deaths over a 5.7 year period in the 18 patients on oral anticoagulants (9 to 10 per cent annual mortality rate). The difference in mortality was statistically significant. However in this last study the patients were not fully randomly allocated as they were in the first three investigations. All four of the above were prospective studies.

Several uncontrolled studies have reported good results. Over an eight year period an annual mortality rate of 2.9 per cent was observed in 17 patients with advanced coronary heart disease who received 20 000 units of heparin twice weekly. Over a five year period in 116 patients on 10 000 units of heparin daily, a 1 per cent annual mortality rate was noted. In a group of 61

patients who received 10 000 units of heparin every other day after an initial larger dose the first four weeks plus a low fat low cholesterol diet only one death was reported over a 3 to 9 year treatment period. However, in this last study although all patients had angina only 19 of the 64 had a prior myocardial infarct.

In two controlled investigations negative results were obtained. In the first heparin 25 000 units twice a week was compared to oral anticoagulants. Therapy was started upon discharge from the hospital after acute myocardial infarction. After the first year heparin was discontinued as the mortality rate was no different on heparin than that of the control group. The authors noted that the exclusion of the deaths in the first six months after infarction would have given results suggesting a favorable effect of heparin. In the second negative trial therapy was also started upon discharge from the hospital after acute myocardial infarction. Patients received 20 000 units of heparin (5 000 unit per ml) twice a week intramuscularly and results were compared to placebo injections. This was a cooperative study involving nine medical clinics but it was unclear as to the details of randomization. Over a 1 to 3 year average period of therapy there was no difference in mortality rate between the two groups.

Careful analysis of all the controlled and randomly allocated studies reveals a logical explanation for the difference in results. In the three that showed a long term protective effect of heparin therapy was started no sooner than six months and usually 1 to 2 years after myocardial infarction. In the two negative reports treatment was begun upon discharge from the hospital after an acute myocardial infarction. It is now appreciated that the majority of deaths in the first year after infarction result from disturbed electrical mechanisms or severe pump failure rather than from progress of the basic atherosclerotic coronary disease. Heparin has no known effect upon myocardial electrical instability. Therefore retardation of the atherosclerotic process would be less apparent in the first 1 to 2 years after an acute myocardial infarct.

Heparin is a very safe medication and few serious reactions have been reported on long term intermittent therapy. With subcutaneous smaller doses given more frequently as 5 000 units daily

or 10 000 to 15 000 units every other day the risk of major hemorrhage or of rebound hypercoagulability is very low. Repeated clotting tests are unnecessary. Many physicians are of the opinion that the prolonged use of heparin causes osteoporosis. A review of all reported cases showed that osteoporotic fractures have only occurred in adults who were given no less than 15 000 units of heparin daily for at least six months. An increased incidence of fractures or of bone pain has not been noted in patients receiving intermittent heparin therapy nor have platelet counts been lowered (unpublished observations). The decrease in circulating antithrombin III recently reported in patients on continuous heparinization was not found when heparin was given intermittently although these subjects did not receive heparin subcutaneously.

In view of the preceding discussion and the facts presented it is hard to understand why this subject has been ignored. For years heparin has not even been mentioned as a possible additional modality in the prophylaxis of atherosclerosis in any leading article nor in statements by official medical advisory committees. Perhaps the answer lies in an earlier excessive claim that a few injections of heparin relieved angina in the majority of patients a claim that was not verified. Perhaps it lies in the widespread unjustified concern about osteoporotic fractures or hemorrhage. Nevertheless although there are many unanswered questions the available evidence deserves attention. Additional controlled clinical studies are needed. The indications for treatment with heparin in relation to atherogenesis are not well established although they have been more fully discussed elsewhere. However it would be unfortunate in view of the unsettled question of the relative merits of medical versus surgical therapy in prolonging the life of patients with coronary disease if an important medical modality were being overlooked.

## Summary

This article reviews the experimental and clinical evidence regarding heparin therapy in the prophylaxis of coronary heart disease. The actions of heparin take place at the vascular endothelium where injected heparin concentrates and within the bloodstream. At the endothelium heparin acts to prevent endothelial injury prevent thrombin generation prevent platelet



adhesion to endothelium and to decrease uptake of serum lipoproteins. Within the bloodstream heparin increases lipoprotein lipase activity and reduces the concentration of atherogenic very low density lipoproteins. The reduction in lipemia enhances oxygen transfer from blood to the tissues and decreases thrombin or ADP induced platelet aggregation. Heparin increases the concentration of high density lipoproteins. It decreases hypercoagulability and inhibits overactivation of serum complement. Heparin reduced atherosclerosis in most studies in cholesterol fed animals. In human subjects who had a myocardial infarct at least one year before the onset of treatment long term intermittent heparin therapy significantly decreased cardiovascular deaths as compared to control groups.

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# American Heart Journal

## Articles to appear in early issues

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# Fundamentals of clinical cardiology

## Acute dissecting aneurysms of the aorta diagnosis and treatment—1979

Myron W Wheat Jr MD

Louisville Ky and St Petersburg Fla

The modern era of the diagnosis and treatment of acute dissecting aneurysms of the aorta was ushered in by DeBakey Cooley and Creech's report in 1965. The twenty four years since 1965 have seen tremendous strides in both the diagnosis and treatment of this devastating disease process. The mortality rate has been decreased from over 90% at 3 months in untreated patients with acute dissecting aneurysms of the aorta<sup>1</sup> to 20 to 35% today utilizing current methods of diagnosis and treatment.

The purpose of this report is to detail the diagnosis and treatment of acute dissecting aneurysms as it stands today 1979. The discussion does not include dissecting aneurysms of vessels other than the aorta and does not include dissecting aneurysms as the result of trauma produced by external forces or introduced at the time of catheterization or cardiopulmonary bypass.

### Incidence and pathogenesis

The incidence of occurrence of acute dissecting aneurysms of the aorta will vary some from one locality to another depending on the age and racial distribution of the population. The acute dissecting aneurysm probably occurs at a rate of 5 to 10 per million population per year as a general average—or at least two to three times the incidence of the rupturing abdominal aortic aneurysm.<sup>1</sup> Pate and colleagues<sup>2</sup> have estimated as high as 20 patients per million population in the Memphis area. Clearly the acute dissecting aneurysm is not only the most common but the most lethal catastrophe that can involve the aorta.

Dissecting aneurysms occur with greatest frequency in the male population from 50 to 70 years of age. In our own series 17% of the patients were over 70.<sup>3</sup> Dissecting aneurysms are relatively rare in patients under 40 except in those with a familial predisposition 'Marfan's syndrome'<sup>4</sup> or congenital heart disease such as coarctation of the aorta and/or bicuspid aortic valve.<sup>5,6</sup> As many as 50% of dissecting aneurysms seen in patients under the age of 40 may occur in pregnant women.<sup>11</sup>

Hurst and associates<sup>7</sup> and Pate and colleagues<sup>2</sup> believe there is no racial predilection for dissecting aneurysms. However both Levinson and co-workers<sup>8</sup> and Rider and colleagues<sup>12</sup> noted an increased incidence of dissecting aneurysms in the Negro. In our own series<sup>3</sup> 60% of the patients were black whereas the hospital population was 30% black as was the surrounding community from which patients were drawn. The higher incidence of dissecting aneurysms in the Negro may be related to their increased frequency of hypertension.

### Pathogenesis

Recent reports by Schlattmann and Becker<sup>9,10</sup> have challenged previous concepts concerning changes in the media of the aorta and the relationship of those changes to acute aortic dissection.

Previously medial degeneration—Erdheim's cystic medial necrosis—loss of smooth muscle cells and elastic tissue in the media—scarring, fibrosis and hyaline like changes—was believed to be the specific basic underlying process in acute dissection. The implication has been that the patient who suffered the acute dissecting process had an aorta with these degenerative medial changes, whereas the patients who did not have an

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dissecting process possessed an aorta essentially normal i.e. without degenerative changes in the media of the thoracic aorta

Schlattmann and Becker<sup>11</sup> studied 100 normal aortas. "The changes of cystic medial necrosis, elastin fragmentation, fibrosis and medionecrosis were tabulated as to distribution and extent. There was a striking correlation with the normal aging process suggesting that medial degeneration probably is more generally present than previously suspected. Their findings showed changes in the media that do correlate with the known frequency of the site of origin of acute dissecting aneurysms. The changes of elastin fragmentation increased in severity with age but the changes were more pronounced in the ascending aorta and aortic arch than in the descending thoracic aorta. Also the inner layers of the media were the most severely affected. They speculate that these changes are related to trauma—the trauma being the forces transmitted by various hemodynamic events related to arterial blood flow.

Fibrosis was shown to increase with age and again the most fibrosis was found in the inner layers of the media and correlated closely with the changes of medionecrosis.

In their findings the thoracic segments were generally more involved than the abdominal segment and the ascending thoracic aorta was involved most frequently and to the severest degree. As in the normal aging aorta within the thoracic wall the inner layers were the most frequently involved.

In summary the changes of medial degeneration are essentially the same as those of medionecrosis. The changes tend to be more frequent and more extensive in the older patient and probably more extensive in patients with hypertension.

It is apparent then that the same features of aortic medial degeneration are found in older persons and in hypertensive patients without dissection. The difference from the aorta with dissection is quantitative rather than qualitative.

In a second study Schlattmann and Becker studied the aortic media from patients with dilated ascending aortas, aortas with complete or incomplete dissection and aortas from patients with Marfan's syndrome. They found only quantitative differences between the so-called normal aging aorta and the obviously diseased aorta with

aneurysms. Schlattmann and Becker considered the changes in the media of the aorta that result in dissecting aneurysms to be the result of the processes of injury and repair initiated by hemodynamic events. These changes they believe occur in varying degrees in all aortas and are not specifically related primarily to dissecting aneurysms of the aorta.

In one autopsy review of 34 cases with Marfan's syndrome dissecting aneurysm was present in 12 or 35%. Medial necrosis of the aorta has also been found in most cases of dissecting aneurysms occurring during pregnancy.

In fewer than 5% the changes are primarily those of syphilis or atherosclerosis. Atherosclerosis does not appear to be a significant factor in the etiology of aortic dissections. Atherosclerotic aneurysms are rare in the ascending aorta where about two thirds of dissecting aneurysms originate. In the distal abdominal aorta where atherosclerotic changes are most pronounced and fusiform aneurysms related to atherosclerosis are common, dissecting aneurysms are rare.

Hypertension present in 87% of our series is the other common finding associated with the development of dissecting aneurysms. However the incidence of dissecting aneurysms in the hypertensive population is not known.

The most likely explanation of the pathogenesis of dissecting aneurysms given considerable added support by the work of Schlattmann and Becker<sup>11</sup> is as follows:

First consider the normal hemodynamic or hydrodynamic forces acting within the aorta with each heartbeat. At an average of 70 heartbeats per minute this propagation of forces occurs just over 1 000 times a day or about 37 million times a year. Viewing this situation externally in relation to the heart and thoracic aorta, what occurs with each heartbeat? The heart, which generates the force and motion, is relatively fixed anteriorly by the sternum and rib cage and posteriorly by the vertebral column. The heart, ascending aorta and aortic arch are suspended much like the pendulum of a clock by the vessels to the head and upper extremities. The thoracic aorta becomes fixed just distal to the left subclavian artery as it becomes rather firmly attached along the left side of the vertebral column.

With each myocardial contraction the heart because of the rigid sternum and vertebral column moves predominantly side to side producing a flexing in the ascending aorta and

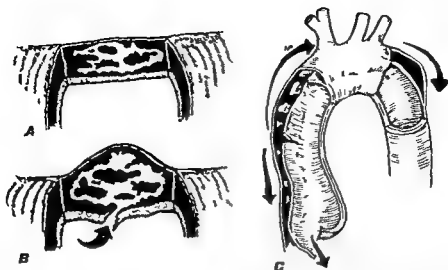


Fig 1 Diagrammatic representation of pathogenesis of dissecting aneurysms. A Degenerative changes in media of aorta sets the stage B Combination of forces produces intimal tear permitting arterial blood to enter weakened media C Resulting dissecting hematoma is propagated in one or both directions by the pulse wave produced by each myocardial contraction and the blood pressure

flexing just distal to the left subclavian artery where mobile aorta joins immobile aorta. The extent and frequency of this flexing action can be simply documented by tracing the outline of the thoracic aorta during systole and diastole in the left anterior oblique projections of aortograms and then superimposing the two tracings. Studies of 42 aortograms showed definite lateral movement of the ascending aorta in 9%. Fifteen aortograms were evaluated for motion just distal to the left subclavian artery and 74% showed definite lateral motion.<sup>3</sup>

Supportive evidence for the tendency of the aortic wall to be disrupted just distal to the left subclavian artery is available from studies of patients suffering deceleration accidents with traumatic rupture of the aorta. Most of the disruptions occur in the area of the isthmus just distal to the left subclavian artery. It is believed that the transverse tears occur in this area because it is the junction of mobile aortic arch with relatively fixed descending thoracic aorta. Pressure from the left lung hilum and a cutting pressure from the recurrent nerve have also been implicated.<sup>4</sup>

The explanation for the higher incidence of intimal tears in the ascending aorta rather than in the descending aorta or abdominal aorta is related to a number of factors.

The hemodynamic events occurring inside the aorta with each cardiac systole probably have their greatest effect on the ascending aorta as

shown by the most marked degenerative changes occurring with age in the ascending aorta.<sup>1, 5</sup> The ascending aorta is also the area where the most external motion and flexion occur with cardiac systole. The traumatic effect of the blood ejected from the heart against the ascending aortic wall may also play a role.

As a result in certain patients as a consequence of many (if not all) of the factors—degeneration of the media, recurring flexion of the aorta, varying tensions applied to the aortic intima by the hemodynamic forces operating within the aorta—an intimal tear occurs 60 to 65% (Fig 1) in the ascending aorta, 5 to 10% in the aortic arch, and 30 to 35% in the first portion of the descending thoracic aorta. The depth of penetration of the tear into the media and to some degree the distance of propagation of the subsequent dissecting hematoma is related to the extent of degeneration in each individual aortic media.

#### Propagation of the dissecting hematoma

Following the intimal tear and the development of a dissecting hematoma, a second set of forces becomes the most important. These forces are those which primarily propagate or continue the dissecting hematoma and include blood viscosity, blood pressure velocity (or shearing forces), turbulence, and steepness of wave  $dP/dT$  max.

Experimental evidence indicates

most important forces propagating the dissecting hematoma are (1) the steepness of the pulse wave<sup>10</sup> and (2) the blood pressure.<sup>1</sup> Therefore the forces that cause the dissection to progress and to eventually rupture leading to the death of the patient are originated by the heart and importantly related to peripheral arterial resistance afterward.

One major force responsible for continuation of the dissection derives from the pulsatile nature of blood flow in large arteries. The reasoning is as follows:

1 The aorta is markedly resistant to static pressure increases.

2 Static pressure provided no pressure gradient as driving forces to induce shear stresses or other stresses on aortic tissue.

3 Experimental models, e.g. Tygon tubing aorta with rubber cement intimas dissect only when the flow is pulsatile and not when the flow is laminar or non turbulent. Experiments with dog aortas show the same relationship to pulsatile flow as do the artificial aortas.

4 Protection from aortic rupture in turkeys with dissecting aneurysms can be accomplished with propranolol, a beta adrenergic blocking agent at a dose that does not affect aortic pressure but does alter the quality of pulsatile blood flow.

Experimental evidence supporting the importance of the blood pressure in the propagation of the dissecting hematoma comes from two principal sources. Carney and associates<sup>11</sup> and Moran and associates<sup>12</sup>. Carney's group showed that in their experimental model in dogs depression of myocardial contractility alone did not prevent progress of the dissection. However controlled hypotension plus depression of myocardial contractility completely inhibited progress of the dissection.

Moran and associates<sup>12</sup> showed that in hypertensive dogs effective control of propagation of the experimental dissecting hematoma required reduction of the arterial pressure as well as reduction in the dP/dt.

### Summary of pathogenesis

The pathogenesis of most dissecting aneurysms of the aorta can be looked upon as occurring as follows:

1 Medial degeneration in the wall of the thoracic aorta sets the stage by decreasing the

cohesiveness of the layers of the aortic wall particularly of the media itself (Fig 1A).

2 Repeated motion of the aorta related to the beating of the heart results in flexion stresses most marked in the ascending aorta and first portion of the descending thoracic aorta 60 to 100 times a minute, 37 million times a year.

3 Hydrodynamic forces in the bloodstream related to the pulse wave propagated by each cardiac cycle as well as the level of the systolic blood pressure act upon the wall of the aorta—most markedly the proximal aorta.

4 A combination of these factors eventually results in an intimal tear which leads to a hematoma dissecting into the media of the aortic wall for varying depths (Fig 1B). Hydrodynamic forces in the bloodstream primarily related to the steepness of the pulse wave  $dP/dt_{max}$  as well as the blood pressure (Fig 1C) continue the propagation of the dissecting hematoma until rupture occurs either (1) back into the lumen of the aorta resulting in a spontaneous cure, a rare but documented occurrence<sup>13</sup> or more likely (2) rupture into the pericardium or pleural cavity leading to death within 30 days in most instances.

### Diagnosis

**Clinical picture.** Pain is the single most important and outstanding feature of the patient who presents with an acute dissecting aneurysm of the aorta. The pain is usually excruciating and may be described as sharp, knifelike, tearing or ripping in nature. The pain is usually the most severe the patient has ever experienced and is difficult if not impossible to relieve with opiates.

The pain most commonly is located in the anterior chest or in the back between the shoulder blades. The pain may begin in the chest, progress to the back and down along the spine. The pain may occasionally mimic the pain of angina pectoris with radiation into the shoulders and arms rarely to the jaw or neck.

Two thirds to three fourths of the patients will have hypertension when seen or a history of hypertension in the past, not infrequently having recently discontinued their antihypertensive medication.

There are systolic murmurs over the precordium commonly, but the murmur of greatest importance is the murmur of aortic valve insufficiency usually indicating a Type A (Fig 2).

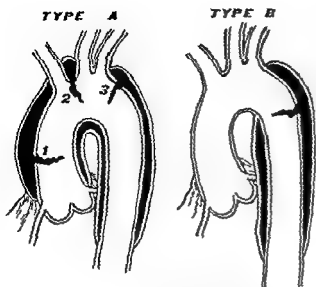


Fig 2 Classification of aortic dissections based upon the presence or absence of involvement of the ascending aorta (modified from Stanford <sup>20</sup>). The primary intimal tear in Type A dissections can be in the ascending aorta (1) and the transverse arch (2) or the descending aorta (3). Includes the DeBakey Types I and II. The primary intimal tear in Type B dissections most commonly is distal to the origin of the left subclavian artery. The dissecting hematoma does not involve the ascending aorta. Includes DeBakey Type III. Acute Type A dissections make up approximately 66%. Type III make up 33%.

dissection with retrograde involvement of the aortic root—a particularly ominous sign.

Murmurs over major branches of the aorta such as the carotid and subclavian arteries are secondary to partial occlusion of the vessel orifices by the dissecting hematoma. There may be a significant difference in blood pressure between the two upper extremities; the left subclavian being the most frequently involved.

Even though the patient may appear to be in shock, his blood pressure will usually be in the hypertensive range or he may show marked hypertension. Occasional patients presenting in frank shock with a low blood pressure may demonstrate a rapid hypertensive response to the transfusion of only one or two units of blood.

In any patient presenting with the onset of sudden severe pain involving the thorax, abdomen or back, the diagnosis of acute dissecting aneurysm of the aorta should be seriously considered. Peripheral pulses that come and go disappear abruptly and acute neurological deficits are helpful but only present in 20 to 25% of cases.



Fig 3 Diagrammatic representation of the usual path of dissecting hematoma (shaded area) originating from an intimal tear in the ascending aorta.

Once the diagnosis of acute dissecting aneurysm of the aorta is seriously entertained, the next step is a chest roentgenogram followed by angiographic studies.

#### Roentgenographic findings in dissecting aneurysms of the aorta

A chest roentgenogram which should be taken as soon after admission as possible usually will show widening of the mediastinum. However, lack of mediastinal widening does not rule out dissecting aneurysm since this sign may be present in only 40 to 50% of cases. Classically, the mediastinum will bulge to the right with dissection of the ascending aorta and will show widening of the mediastinum on the left with involvement of the descending thoracic aorta. Obliteration of the aortic knob with displacement of the trachea to the right are helpful signs.<sup>21</sup> Previous chest roentgenograms if available are very useful for comparison.

Mediastinal widening therefore is a highly

suggestive but non diagnostic sign of acute aortic dissection. Neoplastic hemorrhagic<sup>3</sup> or inflammatory processes involving the mediastinum can produce similar widening. Intramediastinal widening from leaking saccular aneurysms of the thoracic or upper abdominal aorta, can produce subadventitial dissecting hematomas. These hematomas which do not involve the media of the aortic wall and therefore are not true dissecting aneurysms can result in false positive diagnoses even after aortography. Calcium in the wall (intima) of the aorta with obvious widening beyond the calcium of at least 4 to 5 mm is usually considered diagnostic but only rarely present.

Chest roentgenograms also may show pleural effusions most commonly on the left which are usually serous. A serosanguineous pleural effusion does not necessarily mean that there is rupture or impending rupture of the aneurysm. The adventitia can weep red blood cells from the dissecting hematoma producing a serosanguineous pleural effusion without an actual rupture of the wall of the aorta. However a frankly bloody effusion is an obvious ominous sign indicating true leakage with impending rupture.

The typical path of the dissecting hematoma of the aorta is shown in Fig 3. When the dissection begins in the ascending aorta it is usually to the right and anterior just distal to the level of the coronary artery ostia. As the hematoma advances into the arch it is posterior and superior. In the descending thoracic aorta it is posterior and to the left. There is a higher incidence of dissection into the left renal artery and the left iliofemoral system than into the right.

The manifestations of dissecting aneurysms of the aorta on chest roentgenograms can be summarized as follows:

- 1 Widening of the aortic arch
- 2 A change in configuration of the aorta on successive roentgenograms
- 3 Obliteration of the aortic knob with displacement of the trachea to the right
- 4 A localized hump on the aortic arch
- 5 Disparity in size of the ascending and descending thoracic aorta
- 6 Aortic wall thickening indicated by widening of the aortic shadow out of normal calcification (rare)

Since chest roentgenograms are not diagnostic aortograms should be performed within 4 hours after admission to either confirm or rule out the diagnosis.

### Technique of aortography

The technique of aortography in patients suspected of having dissecting aneurysm of the aorta is as follows:

The Seldinger percutaneous technique<sup>7</sup> using a femoral artery is followed using a pigtail or O'Keefe catheter. The catheter is passed over a J shaped guidewire with a 3 to 9 inch floppy tip. The more tortuous the iliac artery and aorta the greater the need for a long flexible-tipped guide wire. Careful manipulation together with the floppy J tipped guidewire catheter makes this a safe procedure. This is virtually no danger of elevating a plaque and initiating a dissection.

Hypaque M 75% is used as a contrast medium. After a test hand injection a Viamonte Hobbs pressure injector is used for the definitive studies. The amount used totals 130 to 150 ml for the two three or four separate injections. The first injection is in the aortic root to look for the intimal tear and to evaluate the status of the aortic valve and the ostia of the coronary arteries. Initially views are taken in the anteroposterior (AP) and the lateral projections with exposures taken alternately in each view. The left anterior oblique position is used if the initial AP and lateral projections are not adequate. Several minutes after the first injection the abdomen is fluoroscoped to obtain some idea of the location of the contrast material.

After the first injection (we usually wait 10 or 20 minutes between injections) the films are evaluated and frequently the entire thoracic aorta is found to be adequately outlined. The catheter is then withdrawn to just below the diaphragm where a second injection is made to determine the distal extent of the dissection and the degree of involvement of major abdominal branches of the aorta particularly the renal arteries.

The diagnosis of dissecting aneurysm of the aorta can be made safely in most patients using the transfemoral Seldinger technique as described. However occasionally the transaxillary approach will be necessary. If neither the transfemoral or transaxillary approaches are feasible

or satisfactory the transeptal approach with left atrial angiography has been shown to be satisfactory for visualization of the aortic root.<sup>23</sup>

The diagnosis by angiography is based on

1 Demonstration of two channels

a Linear radiolucency separating the two lumens

b Differences in flow with delayed opacification or delayed washout

2 True lumen only opacified

a Widening of outer extraluminal border of the aorta

b Narrowing of the true lumen with flattening of the side compressed by the dissecting hematoma

c Abnormal catheter recoil and position (only occasionally helpful)

3 In ascending aorta injection into false channel recognized by

a Demonstration of a blind end

b Failure to visualize the sinuses of Valsalva

c Flattening of the medial border of the opacified channel

d Delayed washout in the blind end

Shuford and associates<sup>7</sup> have pointed out some of the problems encountered in making the diagnosis of dissecting aneurysms of the aorta even by aortography. In their series of 44 patients with suspected dissecting aneurysms the diagnosis was confirmed in only 23 by the demonstration of a narrowed true aortic lumen and a false channel. In 11 cases there was no radiologic evidence of dissection. In four patients with dissection the diagnosis was confused by faint false channel opacification, unusual tearing of the intima and/or equal simultaneous opacification of both channels. Layering of contrast material in the descending aorta in a patient with aortic valve insufficiency gave a false positive picture of a false channel. In one patient widening of the mediastinum was secondary to rupture of a thoracoabdominal aneurysm in the mediastinum. In the remaining four patients no definite diagnosis was made.

### Treatment

Ideally the aortogram should demonstrate the site of the intimal tear and the extent of the dissecting hematoma. Once these two pieces of information are available the therapy most

appropriate to that particular patient can be initiated. Today excellent methods are available for definitive treatment of acute dissecting aneurysms of the aorta. These methods involve the use of intensive drug therapy with or without surgical intervention depending on the type of dissecting aneurysm, the age and overall condition of the patient and the hospital setting in which the treatment is to be carried out.

### Treatment modalities available

**Intensive drug therapy** Intensive drug therapy refers to the use of drugs or pharmacological agents to decrease the cardiac impulse ( $dP/dT$  max) and lower the systolic blood pressure as methods of treatment of the patient with an acute dissecting aneurysm of the aorta. Today there are pharmacological agents available which can be used to dramatically lower the blood pressure with little effect on the heart itself. In addition there are other agents which are available such as propranolol with a very selective effect on the heart producing a negative inotropic effect with little peripheral effect. By the use of these agents singly or in combination one can achieve the desired effects of decreasing the steepness of the pulse wave ( $dP/dT$  max) and at the same time dramatically lowering the blood pressure<sup>1</sup> thereby significantly altering both of the forces which must be diminished in order to stabilize or arrest the progression of the dissecting hematoma.

**Surgical therapy** Surgical therapy<sup>2</sup> refers to definitive surgical intervention for the main dissecting process or its complications. Such therapy involves (1) resection and graft replacement rather than fenestration procedures; (2) occasional repair and end to end anastomosis of the aorta; (3) resuspension or replacement of an insufficient aortic valve; and (4) local procedures to restore flow in major branches of the aorta, principally the iliac arteries. The choice and use of these two principal modes of therapy, either exclusively or in combination, must take into account the facilities and surgical expertise in the hospital setting involved.

**Clinical basis** The treatment of the patient with an acute dissecting aneurysm of the aorta initially with drugs followed by prompt diagnosis and then drugs alone or drugs plus appropriate and competent surgical intervention has been in



**Table 1** Summary of 219 patients with acute dissecting aneurysms treated medically (108) or surgically (111)

Author ref	year reported	Ascending aorta (117 patients)				Descending aorta (102 patients)			
		Medical		Surgical		Medical		Surgical	
		Number	Survivors	Number	Survivors	Number	Survivors	Number	Survivors
Dailey <sup>a</sup>	1970	11	3	14	10	5	4	7	5
Attar <sup>b</sup>	1971	5	0	11	5	8	4	10	4
McFarland <sup>a</sup>	1972	6	2	—	—	10	8	—	—
Dalen	1974	9	2	22	17	6	1	8	2
Strong <sup>c</sup>	1974	15	3	9	5	19	15	19	1
Bolooki	1979	2	2	11	13	14	13	3	2
<b>TOTAL</b>		<b>46</b>	<b>12</b>	<b>71</b>	<b>50</b>	<b>50</b>	<b>50</b>	<b>40</b>	<b>20</b>
<b>MORTALITY</b>		<b>74%</b>		<b>30%</b>		<b>20%</b>		<b>50%</b>	

Fourteen patients were initially treated with drugs but in eight the progress of dissection was not controlled which is an indication for surgical intervention. These eight patients are shown as surgical since definitive surgical therapy intervened appropriately.

use for more than 15 years. The therapeutic effectiveness of this approach is well documented by data from a number of different centers (Table I).

Table I is a collection of the results from six separate centers reported since 1970.<sup>2-7</sup> In each center listed an attempt was made to use both intensive drug therapy as well as surgical therapy: the treatment of patients with acute dissecting aneurysms of the aorta. Results reported from groups using only one method or the other, or where the treatment was incomplete or not standardized are not included.

The results (Table I) show convincingly that all patients with acute dissecting aneurysms should be stabilized with intensive drug therapy accurately diagnosed, and then treated appropriately with drugs alone or with drugs plus definitive surgery for localized life threatening complications of the dissecting process.

Seventy-one patients with acute dissecting aneurysms involving the ascending aorta (Type A) (Fig 2) were stabilized, diagnosed and treated surgically with an overall mortality rate of 30%. This compares to a mortality rate of 74% when surgical intervention was not used. On the other hand in the patient with the acute Type B dissection drug therapy alone yielded a survival rate of 80% compared to 30% when surgical intervention was added.

Recently Shumway's group reported their experience with 73 patients with acute dissections (less than 2 weeks old) even over the past 16 years

and treated primarily with surgery.<sup>8</sup> Fifty-three were Type A and 20 were Type B. The operative mortality rate was 34% for A and 45% for B. Patients with acute Type A dissections had an increased operative mortality rate if hypertension was present as it was in 51%.

Major complications that could be directly attributed to the dissecting process also significantly influenced the surgical result. The complications of pleural rupture, aortic regurgitation, pericardial rupture, cardiac tamponade, loss of peripheral pulse(s), loss of arteriographic renal and/or visceral perfusion, cerebrovascular accident, shock, anuria, and arterial thromboembolism, paraplegia and acute myocardial infarction all increased the operative mortality rate. The operative mortality rate for patients with an acute Type A dissection was 14% without any of the above complications as compared to 36% with complications. Acute Type B mortality rate was 11% without versus 73% with. The three most significant complicating factors were cerebrovascular accident, loss of arteriographic vessel or renal perfusion and paraplegia.

Shumway's experience is important because it is a very detailed account of a large consecutive series of acute dissecting aneurysms treated surgically by competent cardiovascular surgeons. The experience documents that the acute dissecting

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Table II Operative mortality rate and sample size in selected series since 1970 the data in the original reports have been reclassified when necessary to correspond with the Stanford Type A and B classification criteria\*

Series	Reference	Year	Acute							
			Type A				Type B			
			Surgical		Medical		Surgical		Medical	
			No	%	No	%	No	%	No	%
Maryland	31	1971	10	60%	5	100%	10	50%	8	50%
UCLA	42	1972	9	89%	—	—	2	50%	—	—
Yale	40	1974	9	40%	15	60%	12	42%	19	21%
PBBH†	39	1974	2*	23%	9	78%	—	70%	6	0%
SUNY Upstate	43	1975	3	100%	2	50%	1	0%	—	0%
THI Houston‡	44	1975	—	—	—	—	49	25%	—	—
Alabama	45	1976	17	24%	17	88%	11	36%	22	39%
THI Houston‡	46	1976	24	21%	—	—	—	—	—	—
Memphis	4	1976	8	63%	20	80%	14	43%	1	100%
THI Houston‡	47	1977	51	18%	—	—	—	—	—	—
Virginia	48	1979	26	73%	3	100%	14	36%	—	65%
Average			119	38%	16	83%	171	38%	67	92%
Present study		1979	53	34%	—	—	20	40%	—	—

\*This table is excerpted from Table IX, ref. 35, with the author's permission.

†Peter Bent Brigham Hospital (3% of 45 total cases were acute).

‡All acute Type B patients failing medical therapy crossed over to surgery.

§Texas Heart Institute: some patients in reference 4 are included in reference 46.

¶Six of 12 deaths had retrograde extensions of their dissections in the perioperative period.

aneurysm continues to be a difficult surgical problem with an overall surgical mortality rate of 34% for patients with acute Type A dissections and 45% for those with Acute Type B dissections. During the most recent 5 years these have been reduced to 27% for Type A and 20% for Type B.

Table II reproduced in part\* from Shumway's report is a compilation of 11 reported series of acute dissecting aneurysms treated since 1970. Series are included that used both medical and surgical therapy, surgical therapy only, and regardless of whether any attempt at a standardized approach to therapy was used. The similarity of results when compared with Table I where only those series where an attempt at a standardized approach to treatment using both medical and surgical therapy are shown is striking.

For acute Type A aneurysms the mortality rate for surgical therapy was 30% in Table I and 38% in Table II; medical therapy 74% in Table I 83% in Table II. Type B surgical therapy was 50%

in Table I and 36% in Table II (45% Shumway), medical therapy 20% in Table I 22% in Table II.

The overall results are remarkably similar and add overwhelming support to the proposed plan of therapy for acute dissecting aneurysms of the aorta.

A recent report from the University of Miami<sup>1</sup> demonstrates further the results that can be obtained by the proper blending of the two available methods of therapy. A protocol was established prospectively and adhered to in all but five patients.

Over a five year period 1972 to 1977 32 patients with the diagnosis of acute aortic dissection confirmed by aortography were admitted to the cardiovascular surgery intensive care unit. All patients with Type A dissections were operated upon after stabilization with drugs and diagnosis by aortography for emergency surgical repair. Type B dissections were treated with drugs alone. Two patients with Type A acute dissections were not operated upon—both patients refused and in

Only the dissection and dissections are reproduced.

Table III Summary of treatment results of 32 patients with acute dissecting aneurysms of the aorta treated 1972-1977 University of Miami, Florida<sup>11</sup>

Site of intimal tear	No.	Emergency surgery (no.)	Operative death (%)	Medical therapy		Delayed repair		Late death (no.)
				Total	Death	Total	Death	
Ascending aorta Type A	15	13	2 (1.3%)	2	0	—	—	13 mos. Stroke 14 1/2 yrs Marfan's
Descending aorta Type B	17	3	1	14	1 (7%)	4	0	

both there was no aortic valve insufficiency and rapid control of hypertension was achieved. Three patients with Type B dissections were operated upon because of enlarging hematoma, small true lumen of descending thoracic aorta, and inability to control hypertension.

The results of treatment of the 32 patients with acute dissection are summarized in Table III. There was a total of 16 patients subjected to urgent surgical repair with three deaths—19%. Sixteen patients were treated with drugs alone with one death—6%. Long term survival (3 years) for patients with Type A dissection treated with drugs plus surgical repair and then long term drug management was 77% (14 of 18) and for patients with Type B dissection treated with drugs alone—91% (20 of 22).

Based on the best available experimental and clinical evidence at the present time, the most rational form of therapy for patients with acute dissecting aneurysms is as follows:

**Treatment in a community hospital.** In the community hospital (without 24 hour expertise available for definitive aortography and without an experienced cardiovascular surgical team) the following treatment should be instituted as soon as the diagnosis of an acute dissecting aneurysm is suspected.

If the patient is hypertensive and in pain, initiate appropriate drug therapy to reduce the blood pressure and control the pain. As soon as the patient's condition is stable and the pain relieved, usually within 1 to 2 hours, move the patient (plus chest roentgenograms) at once by ambulance to the nearest medical center where definitive angiography and cardiovascular surgical expertise are available.

If the patient is not hypertensive but is in pain, reduce systolic blood pressure 20 to 40 mm Hg, carefully observing urine output, stabilize at a pain free level, if possible, and then transfer the patient.

**Treatment in a medical center.** A medical center is defined as having definitive angiographic and cardiovascular surgical expertise available 24 hours a day. Patients suspected of having acute dissecting aneurysms of the aorta should be placed in a cardiovascular surgical intensive care unit where they can be monitored carefully on a minute to minute basis. Other cardiovascular catastrophes such as acute myocardial infarction or cerebrovascular hemorrhage must be ruled out by appropriate studies and consultations.

It is mandatory that these patients be managed and followed on a cardiovascular surgical service. The cardiovascular surgeon must make the decision as to which type of therapy or combination of therapies should be used. All patients should be treated with drugs initially, but certain patients will need to be taken to surgery promptly and the surgeon is the only one who can make the decision as to when it is appropriate to supplement drug therapy with definitive surgical intervention.

In the cardiovascular surgical intensive care unit:

1. Monitor ECG, blood pressure, pulmonary artery wedge pressure, and pulmonary artery pressure via a Swan Ganz type catheter and insert a Foley catheter to monitor the urinary output.

2. Reduce systolic blood pressure to 100 to 120 mm Hg (if appropriate). Use trimethaphan (Table IV) (Arfonad—Table) 1 to 2 mg/ml as intravenous drip acutely and if necessary for 24 to 48 hours with a slow rate to maintain the desired blood pressure. Keep the head of the bed elevated 30 to 45 degrees to enhance the orthostatic effect of the drug.

Sodium nitroprusside (Table IV) should be used only if the patient becomes tachyphylactic to the trimethaphan or does not respond. Nitroprusside, although a potent hypotensive agent, has been shown in the laboratory to definitely

Table IV Drugs used in treating dissecting aneurysms of the aorta

Drug	Mechanism of action	Total effect
Trimethaphan (Arfonad)	Ganglionic blockade direct relaxing effect on vascular smooth muscle histamine release	Decreases myocardial contractility lowers peripheral resistance produced ileus bladder distention pupil dilation
Propranolol (Inderal)	Specifically blocks beta adrenergic stimulation at end-organ receptor (blood vessels heart)	Bradycardia (reduces cardiac output) increases peripheral resistance mild hypotensive effect
Alpha methyl dopa (Aldomet)	Metabolized to alpha methyl norepinephrine a weak neurotransmitter and precursor agent which replaces the more potent norepinephrine at nerve terminal other unknown mechanisms	Sedation little depression reduces peripheral resistance slight bradycardia drug fever abnormal liver function hepatitis
Thiazides (Diuril Hydrodiuril)	Decreased tubular reabsorption of Cl and Na some K is lost results in salt and/or extracellular fluid volume depletion with a possible direct cardiovascular effect	Decrease in blood pressure
Reserpine	Depletes all catecholamines from all tissue stores neurotransmitter (norepinephrine) release diminished after nerve stimulation	Decreases myocardial contractility sedation depression bradycardia (reduces cardiac output) reduces peripheral resistance stimulates gastric secretion
Guanethidine (Ismelin)	Selectively depletes catecholamines from postganglionic nerve terminals particularly in the heart gastrointestinal tract blood vessels but not the central nervous system	Postural hypotension diarrhea bradycardia (reduces cardiac output) decreases peripheral resistance no effect on central nervous system
Sodium nitroprusside (Nipride)	Selectively relaxes vascular smooth muscle	Rapidly lowers blood pressure lowers peripheral resistance reduces cardiac output indirectly by decreasing preload (venous return) produces definite increase in myocardial contractility (dP/dT max)

increase dP/dT. If nitroprusside is to be used pretreatment of the patient with either propranolol methyl dopa or reserpine should be carried out. This pretreatment with a sympathetic blocking agent will diminish the initial reflex adrenergic stimulating effect of nitroprusside which is a result of the direct relaxation of the peripheral vascular bed.

The blood pressure response to trimethaphan is usually rapid and must be regulated carefully. Renal complications as a rule occur only with a profound lowering of the blood pressure for a significant period of time and can be virtually eliminated by careful monitoring of the patient. Usually when the blood pressure is appropriately lowered the patient's pain is dramatically relieved.

The severe pain that patients experience with an acute dissecting aneurysm is most likely secondary to stretch of the adventitia due to the expansion accompanying propagation of the

dissecting hematoma. Relief of the pain by decreasing the forces which are responsible for propagating the dissection i.e. dP/dT max blood pressure etc. indicates arrest and stabilization of the dissecting process. Therefore initial as well as continued relief of pain is probably the single most important clinical sign in the management of these patients.

Once the patient's blood pressure (and cardiac impulse dP/dT max) and pain are brought under control indicating arrest of the progress of the dissecting hematoma and therefore arrest of the threat of rupture with death of the patient and the patient's condition is stabilized the diagnosis must be confirmed or ruled out by aortography.

If the aortogram confirms the diagnosis of an acute dissecting aneurysm then the treatment depends on several factors. The type of the dissecting aneurysm (Fig 2) (Type A indicating that the dissecting process involves the ascending aorta or Type B indicating that the dissecting

process involves the descending thoracic aorta *without* involvement of the ascending aorta) and the age and condition of the patient determine the specific therapy. The differentiating point of most importance is involvement or lack of involvement of the *ascending thoracic aorta*.<sup>22-24</sup>

**Type A Acute**—the ascending aorta is involved by the dissecting process

The intimal tear is usually in the ascending aorta or transverse aortic arch with the *ascending aorta* involved by the dissecting hematoma. The important factor is *involvement of the ascending aorta* by the dissecting hematoma with the threat of retrograde dissection and fatal pericardial tamponade. This type of acute dissecting aneurysm can be corrected surgically today with a mortality rate in the range of 15 to 30%.<sup>25</sup> Therefore the patient with an acute Type A dissecting aneurysm who is otherwise a good surgical risk and under control with suitable drug therapy should be taken to the operating room promptly and appropriate corrective surgery should be performed as soon as the patient's condition can be stabilized with drug therapy and the diagnosis has been confirmed by aortography.

The improvement of surgical results in these patients with this particularly treacherous lesion is due in part to the use of drugs to stabilize the patient's condition, arresting the progress of the dissecting hematoma and taking the patient to surgery on a prompt urgent basis rather than as an unstabilized surgical emergency. The improvement in cardiovascular surgical skills and the management of cardiopulmonary bypass over the past 10 years have been the other significant factors in improving results in the patients with these difficult problems.

**Type B Acute**—the dissecting hematoma is distal to the left subclavian artery

This type of dissecting aneurysm for therapeutic purposes also includes dissections originating in the transverse aortic arch but *without* involvement of the ascending aorta—the key is lack of involvement of the ascending aorta by the dissecting process. All patients with Type B acute dissecting aneurysms should be treated initially with drug therapy.

After the aortogram establishing the diagnosis

of an acute Type B dissection the patient should be returned to the cardiac surgical intensive care unit.

1 Continue to regulate the blood pressure with trimethaphan.

2 Administer alpha methyl dopa 250 to 500 mg intramuscularly or intravenously every 4 to 6 hours (Table IV).

3 Continue to monitor ECG, blood pressure, peripheral pulses, urinary output and examine stools for blood.

4 Take daily chest roentgenograms to check for progressive mediastinal widening or changes in thoracic aortic contour and for pleural fluid.

If the patient's condition stabilizes the patient is not in pain and there is no evidence of progress of the dissection, drug therapy should be continued into the chronic long term phase.

Surgical intervention for the Type B acute dissecting aneurysm is indicated when any of the following occurs:

1 Progress of the dissecting hematoma as shown by (a) significant increase in the size of the dissecting hematoma while the patient is receiving maximal intensive drug therapy, (b) appearance of or changing murmur over aortic branches of the aorta or the aortic valve area indicating continued progress of the dissecting hematoma with involvement of the ascending aorta, (c) signs of compromise or occlusion of a major branch of the aorta such as deepening coma, stroke, painful cool extremity, marked decrease in or cessation of urinary output.

2 Impending rupture of the dissecting hematoma as evidenced by (a) acute irregular aneurysm by aortography, (b) significant increase in size of the aneurysm within hours, (c) blood in the pleural space or pericardium, (d) lack of ability to control pain with intensive drug therapy.

3 Inability to bring blood pressure or pain or both under control within 4 hours after start of intensive drug therapy.

**Summary of treatment indications for intensive drug therapy**

1 Drug therapy is the initial treatment of choice in all patients with acute dissecting aneurysms.

2 Type B dissecting aneurysm do not involve most of the ascending aorta by the dissecting process.

3 The site of the intimal tear cannot be identified.

tified on the aortogram and there is no involvement of the ascending aorta

4 The site of origin is in the transverse arch without extension of dissecting hematoma into the ascending aorta

5 Patients who are poor surgical risks in general

■ Stable chronic aneurysms onset more than 14 days earlier

7 Community hospital that lacks facilities for definitive aortography and experienced cardiovascular surgical team

8 Failure of opacification of the false channel

#### Summary of treatment indications for definitive surgical therapy

1 Type A dissecting aneurysm the ascending aorta is involved by the dissecting hematoma  
2 Aortic valve insufficiency secondary to dissecting aneurysm (means ascending aorta is involved also)

3 Localized or impending rupture

4 Progress of the dissecting hematoma while receiving maximal drug therapy

5 Compromise or occlusion of a major branch of the aorta

6 Acute saccular aneurysm

7 Blood in pleural space or pericardium or both

8 Inability to relieve and control pain

■ Inability to bring blood pressure and cardiac impulse under control within 4 hours

#### Follow up therapy

The management and follow up after the acute phase is the same whether drugs alone or drugs plus surgery have been used. Drug therapy should be continued in patients who have undergone surgical correction for dissecting aneurysms. The underlying pathologic process—*aortic medial degeneration* is still present and will tend to progress.<sup>10,11</sup> These patients are prone to have either a localized redissection or to sustain a second separate dissection of the aorta.

As the patient's clinical status stabilizes and the administration of intravenous agents—*frumethaphan* or *sodium nitroprusside*—is discontinued the patient should be transferred to routine hospital floor care for progressive ambulation and final regulation of drugs. During the first week of therapy in the hospital daily chest roentgenograms

grams to check for progressive mediastinal widening or changes in thoracic aortic contour and pleural fluid are indicated.

Orthostatic hypotension is frequently observed at this time and the drug dosages must be regulated to maintain the desired hemodynamic effects while permitting relatively normal activity. I prefer to discharge these patients with a systolic blood pressure no higher than 130 mm Hg supine and a minimal oral dosage of 60 mg of *propranolol* or 500 mg of *alpha methyldopa* per day. *Reserpine* up to 0.5 mg/day and *guanethidine* are still used occasionally. The addition of one of the thiazide diuretics is also frequently useful (Table IV). The physician should not hesitate to combine several drugs in seeking the best combination producing the desired blood pressure and inotropic control with the fewest undesirable side effects in a particular patient (Table IV).

Follow up care consists of a first visit to the physician at a one month interval and then regular visits at three month intervals. At each visit these patients are checked for a history of pain, the presence or absence of peripheral pulses and murmurs, the level of blood pressure, murmurs in the aortic area particularly that of aortic valve insufficiency, prosthetic valve sounds if the aortic valve has been replaced and the status of the chest roentgenograms.

The chest roentgenograms are important for continued evaluation of the size of the aneurysm or the area of graft insertion or both or of the aortic anastomosis. Localized saccular aneurysms can develop in as many as 14 to 25%<sup>12</sup> of patients with Type III aneurysms in the chronic follow up phase. When saccular aneurysms are suspected they should be documented by aortograms and promptly replaced with a tubular prosthesis.

If circumstances permit it is worthwhile to teach a member of the family to check and record the patient's blood pressure on a daily basis. The blood pressure check should be performed at the same time each day with the patient both supine and standing. A daily record available for review at each visit is helpful for blood pressure regulation.

I do not know of a single instance of a patient with an acute dissecting aneurysm treated with drugs and followed continuously in the manner outlined above in whom the aneurysm has ruptured abruptly. In my experience impending

trouble in the follow up period has always been evident on the basis of (1) signs and symptoms of progressive aortic valve insufficiency (2) chest or back pain or (3) enlargement of a saccular area of the aneurysm visible on chest roentgenogram. These findings have allowed sufficient time for appropriate aortography followed by elective surgical therapy when indicated.

## Prognosis

Physicians using the approach to the treatment of acute dissecting aneurysms described here should achieve an over all hospital survival rate of at least 70 to 80% depending upon the patient population. In those patients with acute dissecting aneurysms of the aorta treated with drug therapy alone one should anticipate the development of localized saccular aneurysms in 14 to 20% of patients and progressive aortic valve insufficiency ultimately requiring aortic valve replacement in about 10% following discharge from the hospital. Those patients whose dissecting hematoma does not opacify an initial aortography and who are or should be treated with drugs alone can be expected to do well without the development of sacular aneurysms. In those patients with aneurysms involving the ascending aorta Type A whose ascending aorta is either anastomosed or replaced with or without aortic valve replacement the results are good for at least 5 to 7 years.

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## Clinical pharmacology of the new beta-adrenergic blocking drugs Part 11 Effects of oral labetalol in patients with both angina pectoris and hypertension a preliminary experience

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Beta adrenoceptor blocking drugs are widely accepted for the treatment of hypertension, arrhythmias and angina pectoris.<sup>1,2</sup> Labetalol 5 (1 hydroxy 2 (1 methyl 3 phenylpropyl) amino) ethyl salicylamide (Fig. 1) is a recently developed drug which like propranolol blocks both beta<sub>1</sub> and beta<sub>2</sub> vascular and bronchial receptors.<sup>3,4</sup> However, labetalol is unique in that it also has both alpha adrenergic blocking properties and direct vasodilating activity.<sup>5,6</sup> The beta blocking potency of labetalol is four to 16 times that of its alpha blocking potency.

Alpha adrenergic blocking drugs have limited therapeutic application compared to beta adrenoceptor blocking drugs. This may be in part because of the unwanted effects of reflex tachycardia and orthostatic hypotension which can aggravate coronary artery disease. In selected patients with variant angina, alpha blocking agents have been useful as adjunctive therapy. Patients with coronary artery disease develop

increased cardiovascular resistance following the cold pressor test.<sup>7</sup> Phentolamine reverses this effect. This latter finding raises the possibility that alpha adrenoceptor blockade may play a role in the prevention of myocardial ischemia.<sup>8,9</sup>

Labetalol, an alpha beta blocker, has been shown to be a potent antihypertensive drug.<sup>10,11</sup> Intravenous administration of labetalol in patients with angina pectoris resulted in a marked increase in exercise tolerance.<sup>12</sup> In the present pilot study the effects of oral labetalol in patients who have both angina pectoris and essential hypertension were assessed.

### Methods

**Patients.** Six male patients with stable angina pectoris and systemic hypertension were entered in the study. The average age was 55 years (range 47 to 59 years). The diagnosis of angina pectoris was established by clinical history, symptoms and response to sublingual nitroglycerin and by the development of typical angina pectoris with the treadmill exercise test. In addition, five of the six patients had an exercise induced ECG ST segment depression of at least 1 mm of the ischemic type. The diagnosis of coronary artery disease was made by coronary angiography (a stenosis compromising the lumen of at least one major coronary artery by more than 75%) in three patients and by a previously documented myocardial infarction in the other three. All patients

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had to have at least five attacks of angina pectoris a week for one month with no evidence for an accelerated course. Hypertension was documented in all patients by an average 3 minute standing diastolic pressure of  $\geq 90 \leq 110$  mm Hg (using Korotkoff Phase V) on at least two separate outpatient visits while untreated.

Patients with the following conditions were excluded from the study: coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate  $< 50$  beats/minute), intermittent claudication, and either myocardial infarction or coronary artery bypass within 3 months.

None of the patients received medication during the trial other than the study drug and sublingual nitroglycerin. Written informed consent was obtained in all instances.

**Experimental design.** This study was divided into three periods. A three week placebo period in which patients received placebo\* three times daily (t.i.d.) was followed by a four week labetalol treatment period. The dose of labetalol was titrated weekly (100 to 400 mg t.i.d.) to achieve the optimal antihypertensive effect and improvement in the patient's anginal symptoms. The optimal antihypertensive effect was defined as an average 3 minute standing diastolic blood pressure of  $< 90$  mm Hg and at least a 10 mm Hg reduction from placebo baseline. Improvement in angina was defined by a significant decrease in the number of anginal attacks and by a significant increase in exercise tolerance. If the antihypertensive goal were achieved at a lower dose than the maximum, but the angina did not improve, the dose of labetalol was to be increased. However, this increase was only to be made if it was felt that the patient could tolerate it without developing clinical signs of hypotension. At the end of this four week therapeutic period, the dose of labetalol was tapered over a two day interval. The patient was reassessed 1 to 4 days after cessation of labetalol and again in one week.

**Methods of observation.** All patients kept a detailed daily record of the angina attacks they experienced, the number of nitroglycerin tablets taken, and an estimation of the physical activity for that day. Every week the patients were evaluated with a detailed history and physical examination which included measurements of

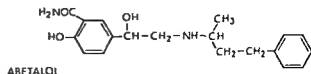


Fig 1 Chemical structure of labetalol

supine and standing (3 minute) heart rate and blood pressure. Blood pressure and heart rate determinations were always made 2 hours after ingestion of placebo or labetalol, which is the time of the peak pharmacological effect of labetalol.<sup>13</sup> Patients also underwent multistage treadmill exercise studies (Bruce Protocol<sup>14</sup> each week). Complete blood counts, urinalyses, chest roentgenograms, resting electrocardiograms and biochemical blood screening tests (total protein, albumin, calcium, phosphate, cholesterol, triglycerides, urea, acid blood, urea nitrogen, glucose, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, SGOT, SGPT, CPK, LDH, CO<sub>2</sub>) were performed pre- and post labetalol treatment.

**Exercise tests.** Multistage exercise testing following the Bruce protocol<sup>14</sup> was performed weekly with the use of a treadmill. The blood pressure was measured every minute during exercise by the auscultatory method and the ECG was monitored on the oscilloscope. The end point of exercise was angina pectoris defined by the patient's typical chest pain discomfort. An abnormal electrocardiographic response was defined as a flat or downsloping ST segment depression of 1 mm of 0.08 seconds duration after the terminus of the QRS complex with the P-Ta segment as the baseline of reference.

Work performance was expressed in total minutes of treadmill exercise. The product of heart rate and systolic blood pressure, an indirect index of myocardial oxygen consumption<sup>15</sup> was calculated from measurements obtained at each one minute measuring interval.

**Statistical analysis.** Group means are presented with the standard error of the mean as the index of dispersion. Comparison between treatment phases were made using Student's paired two-tailed t test.

## Results

**Effects on resting blood pressure and heart rate (Table I).** There was a statistically significant reduction in the supine and standing systolic and

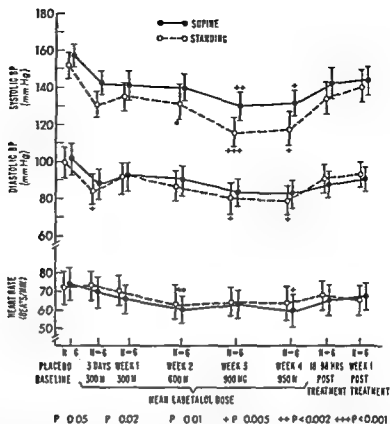


Fig 2 Effects of placebo and labelamol on resting supine and standing blood pressure and heart rate Compared to placebo a significant decrease in systolic and diastolic blood pressure is seen with initiation of labelamol therapy (300 mg/day) an effect which is augmented when higher doses of the drug are used A significant decrease in supine heart rate is seen with labelamol 600 to 900 mg/day compared to placebo There is no rebound in heart rate and blood pressure above placebo values one week post withdrawal

Table 1 Effects of labelamol on resting heart rate and blood pressure in patients with both angina pectoris and hypertension

	Baseline (placebo) N = 6	Peak dose labelamol (mean dose 950 mg) N = 6	Difference	Significance
<b>Supine</b>				
Heart rate (beats/min)	76.8 ± 4.7	63.9 ± 3.5	-12.9 ± 2.5	p < 0.005
Systolic BP (mm Hg)	158.8 ± 4.0	135.3 ± 9.9	-23.5 ± 4.5	p < 0.005
Diastolic BP (mm Hg)	103.64 ± 1.6	87.1 ± 2.1	-16.5 ± 3.6	p < 0.01
<b>3 minute standing</b>				
Heart rate (beats/min)	75.9 ± 5.1	67.7 ± 3.1	-8.2 ± 4.3	NS
Systolic BP (mm Hg)	154.6 ± 6.1	121.6 ± 7.9	-33.0 ± 5.7	p < 0.005
Diastolic BP (mm Hg)	102.0 ± 1.7	83.1 ± 4.1	-18.9 ± 3.1	p < 0.005

Mean ± standard error of the mean

diastolic blood pressure from placebo baseline (Fig 2) After four weeks of labelamol treatment mean supine systolic blood pressure was reduced by 23.4 mm Hg and the standing systolic blood pressure fell by 33 mm Hg While there was a postural fall in systolic pressure this was not statistically significant Mean supine diastolic

blood pressure was reduced by 16.5 mm Hg and standing diastolic blood pressure was reduced by 18.9 mm Hg Supine heart rate fell by 12.9 beats per minute which was statistically significant (p < 0.005) The standing heart rate was approximately 5 beats/minute higher than the supine heart rate The standing heart rate fell 8.3 beats

Table II Effects of labetalol on exercise tolerance and determinants of myocardial oxygen consumption

	Exercise time (min) N = 6	Exercise peak systolic pressure mm Hg N = 6	Exercise peak heart rate beats/min N = 6	Exercise peak rate pressure product N = 6
Baseline (placebo)	4.3 ± 0.9	188.3 ± 18.9	124.5 ± 9.1	2308 ± 33.6
Peak dose labetalol (mean dose 950 mg)	6.3 ± 0.4	148.3 ± 17.8	118.0 ± 6.2	1770 ± 25.60
Difference	+2.0 ± 0.6	-39.3 ± 7.0	-6.5 ± 5.1	-5003 ± 1600
Significance	p < 0.02	p < 0.005	NS	p < 0.001
	HR change from rest to Stage I beats/min N = 6	HR change from rest to Stage II beats/min N = 4	Systolic BP change from rest to Stage I N = 6	Systolic BP change from rest to Stage II N = 4
Baseline (placebo)	34.7 ± 6.6	42.0 ± 7.9	15.5 ± 7.9	38.7 ± 11.3
Peak dose labetalol (mean dose 950 mg)	29.5 ± 3.5	41.3 ± 4.7	5.0 ± 3.9	16.8 ± 9.9
Difference	-5.2 ± 5.3	-0.7 ± 3.9	-10.5 ± 6.3	-22.0 ± 5.6
Significance	NS	NS	NS	p < 0.05

Mean ± standard error of the mean

per minute but this was not a statistically significant fall

**Effects on angina pectoris** Subjective improvement was found in a significant reduction ( $p < 0.05$ ) in the number of angina pectoris attacks (and nitroglycerin consumption) per week ( $8.5 \pm 2.6$  attacks at baseline and  $1.0 \pm 0.6$  attacks after four weeks of labetalol treatment). The quality of life of the patients was enhanced they reported increased ability to perform activities of daily living. All patients were Functional Class III (American Heart Association Criteria) on entry into the study and became Class II after four weeks of labetalol.

**Stress test results** (Table II and Fig. 3) The resting heart rate prior to the exercise stress test was decreased from placebo baseline by  $10 \pm 3.5$  beats/minute which was statistically significant ( $p < 0.02$ ). The heart rate was also significantly reduced at Stage I ( $p < 0.02$ ) but not at Stage II of the Bruce protocol. While there was an absolute reduction in heart rate there was no inhibition of the exercise induced increases in heart rate as measured by the beats/minute increase in heart rate from rest to Stage I and II at baseline and after four weeks of labetalol ingestion. The peak heart rate achieved with exercise after labetalol therapy was not significantly different from placebo baseline even though total exercise time increased by 45%.

The resting systolic blood pressure prior to the

stress test was significantly reduced ( $p < 0.001$ ) as was the systolic blood pressure at stage I and II ( $p < 0.005$ ). However a significant inhibition of exercise induced increases in systolic blood pressure was found only at stage II ( $p < 0.05$ ) no significant inhibition was found Stage I. At Stage I the mean reduction in the rise from rest with placebo to the rise after labetalol was  $-10.5$  mm Hg and the significant inhibition at Stage II was  $-22.0$  mm Hg.

With significant reductions in both heart rate and systolic blood pressure it is not surprising that the rate pressure product (heart rate  $\times$  systolic blood pressure) is also significantly reduced at rest and during exercise following labetalol treatment ( $p < 0.02$ ). It should be noted that even though the peak rate pressure product is significantly less ( $p < 0.02$ ) than at placebo baseline the patients had a significant increase in their exercise tolerance.

At the endpoint of the stress test there was no significant decrease in the magnitude of the ST segment depression. However it should be remembered that exercise time significantly increased. These findings are best illustrated in a patient with three vessel coronary artery involvement (Fig. 4).

**Effects of Labetalol Withdrawal** (Table III Fig. 3) One week following labetalol withdrawal there was a return of resting blood pressure, heart rate and rate pressure product towards placebo

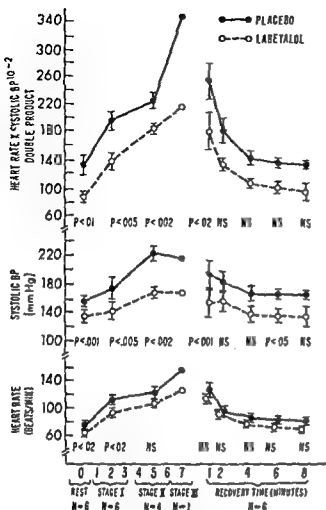


Fig 3 Effects of placebo and labetalol on systolic blood pressure, heart rate, and rate-pressure product during rest, exercise, and recovery. Systolic blood pressure, heart rate, and rate-pressure product with exercise (Stage I Bruce) are significantly lower in labetalol treated patients when compared to placebo. Following exercise, the time for recovery to baseline heart rate and blood pressure is similar with placebo and labetalol.

values without evidence of rebound. Though not significant because of a high variability, the mean values following withdrawal were lower than at placebo baseline.

An increase in the frequency of anginal attacks and a reduction in exercise tolerance occurred following withdrawal when compared to the labetalol treatment phase. No patients developed unstable angina pectoris or an acute myocardial infarction during the one week withdrawal interval.

**Adverse experiences.** Two patients complained of mild dizziness within one day of initiating labetalol treatment, a reaction which was self-limited and not seen later with higher doses. One

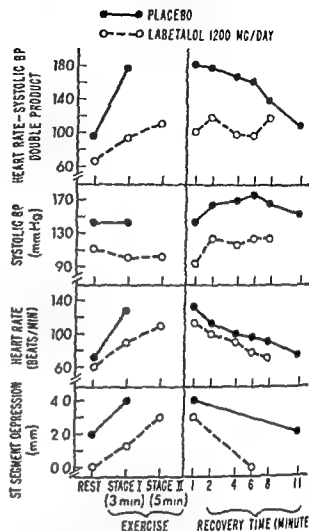


Fig 4 The effects of placebo and labetalol on systolic blood pressure, heart rate, rate-pressure product, and FCC ST segment depression during rest, exercise, and recovery in a representative patient (C M).

patient complained of mild fatigue at the highest labetalol dose, which disappeared when the dose was reduced; this same patient complained of decreased libido without ejaculatory dysfunction.

Fundoscopic examinations did not detect any sign of oculotoxicity during the trial.

There were no abnormalities found in the tests of liver and renal function. There was no significant difference between triglyceride and cholesterol levels after labetalol treatment when compared with placebo.

## Discussion

Labetalol, a unique beta-adrenergic blocking agent with alpha-adrenergic blocking properties, is the forerunner of a new pharmacologic class of

Table III Effects of labetalol withdrawal (1 week post therapy) on blood pressure and heart rate compared to control

	Baseline (placebo) N = 6	Labetalol withdrawal (1 week post therapy)	Difference	Significance
<i>Supine</i>				
Heart rate (beats/min)	76.8 ± 4.7	71.4 ± 3.4	-5.4 ± 6.0	NS
Systolic BP (mm Hg)	158.8 ± 4.0	149.0 ± 4.6	-9.8 ± 5.9	NS
Diastolic BP (mm Hg)	103.6 ± 1.6	95.8 ± 4.4	-7.8 ± 4.7	NS
<i>3 minute standing</i>				
Heart rate (beats/min)	75.9 ± 5.1	72.5 ± 4.6	-3.4 ± 6.1	NS
Systolic BP (mm Hg)	154.6 ± 6.1	144.9 ± 8.9	-9.7 ± 6.8	NS
Diastolic BP (mm Hg)	102.0 ± 1.7	97.2 ± 5.4	-4.8 ± 4.6	NS

Mean ± standard error of the mean

compounds Beta adrenergic blocking drugs have an established position in the treatment of essential hypertension and angina pectoris.<sup>1,2</sup> Recent evidence suggests that alpha adrenergic blockade may play a role in the prevention of myocardial ischemia by inhibiting neurogenic vasoconstriction in coronary arteries.<sup>3-10,20</sup> Reflex tachycardia and orthostatic hypotension have precluded their use as the sole agent in angina pectoris.<sup>2</sup> Thus there is a potential advantage to the use of labetalol in the treatment of angina pectoris.

Labetalol is an antihypertensive agent of considerable potency<sup>1,2</sup> and appears to be more effective than propranolol in reducing blood pressure.<sup>21,22</sup> Labetalol has been shown to be efficacious in hypertensive crises<sup>23</sup> pheochromocytoma<sup>24</sup> and in many cases of drug resistant hypertension.<sup>25</sup>

Despite its widespread application in hypertensive disease there has been little experience in patients with angina pectoris. When administered intravenously to patients with angina pectoris it produced a significant increase in exercise tolerance but without any clearcut dose response relationship.<sup>4</sup> Normotensive patients with coronary artery disease receiving 200 mg of labetalol daily demonstrated increased exercise tolerance and electrocardiographic evidence of improvement when compared with placebo.<sup>26</sup>

The results of our preliminary study show that oral labetalol is an effective therapy for patients with both angina pectoris and hypertension. The drug reduced resting systolic and diastolic blood pressure both supine and standing upon initiation of therapy (100 mg t.i.d.). An augmentation of the antihypertensive effect was seen with

higher doses (200 to 400 mg t.i.d.). Unlike pure alpha adrenergic blocking agents<sup>21</sup> labetalol reduced the blood pressure without increasing the heart rate. There was a slight reduction in standing heart rate and a significant reduction in supine heart rate. The effects of the drug on systolic blood pressure were more pronounced in the standing position. The differences between standing and supine systolic blood pressure determinations following labetalol may relate to the vasodilatory effects of alpha adrenergic blockade which are more important in the standing position. Supine heart rate is significantly reduced while standing heart rate is not. The differences between standing and supine heart rate determinations following labetalol may relate to a compensatory increase in rate with erect posture. Postural hypotension was not seen with labetalol probably because the drug is a relatively weak alpha adrenergic blocker compared to phentolamine. It follows then that the components of the reduction in rate pressure product with labetalol in the supine and standing positions differ in the upright position: there is a greater reduction in systolic blood pressure and a lesser reduction in heart rate. On the other hand in the supine position there is a lesser reduction in systolic blood pressure and a greater reduction in heart rate.

There was a significant reduction in spontaneous attacks of angina pectoris and a significant increase in exercise tolerance with the peak labetalol dose.

At a comparable level of exercise (Stage I—Bruce) the heart rate blood pressure and rate pressure product with labetalol were reduced compared to placebo. The peak heart rate

blood pressure product achieved with exercise was lower following labetalol than with placebo despite a marked increase in exercise tolerance. Thus in this small series labetalol appears to be an effective antianginal agent increasing exercise tolerance while reducing myocardial oxygen demands.

There were no intolerable adverse reactions noted with the drug and one week following labetalol withdrawal there was no hyperadrenergic rebound state demonstrable. Following withdrawal the heart rate and blood pressure were slightly lower (not significant) than baseline placebo levels (although significantly higher than with labetalol). This might reflect a prolonged action of the drug despite its short plasma half life,<sup>14</sup> or a training effect in the patients.

Beyond the improvement in exercise tolerance and reduction in angina attacks there are other potential therapeutic advantages in the use of alpha beta adrenoceptor blocking agents in angina pectoris. Since neurogenic vasoconstrictor impulses to the coronary resistance vessels are transmitted through sympathetic nerves acting upon alpha adrenergic receptors in the coronary vascular bed there may be an important role for alpha adrenergic blocking drugs in the prevention of coronary spasm and in the preservation of restricted coronary blood flow.<sup>15-17</sup> This was suggested in a study by Mudge and associates where phentolamine was shown to block reflex coronary vasoconstriction regularly elicited by the cold pressor test. Orlick and colleagues<sup>18</sup> also demonstrated that alpha adrenergic blockade was a useful adjunct in selected patients with variant angina.

Beta adrenoceptor blocking drugs have been shown to decrease coronary blood flow in patients.<sup>19</sup> Stimulation of beta<sub>2</sub> receptors which induced vasodilation in coronary arteries can be blocked by propranolol. Indeed blockade with nonselective beta adrenergic blockers may actually be detrimental in patients in whom ischemia is due to reduced oxygen delivery secondary to coronary spasm. Non selective beta adrenoceptor blockade may allow the unopposed influence of coronary vasoconstrictor impulses to prevail. Coronary blood flow was found to increase following intravenous labetalol administration in dogs.<sup>21</sup> Labetalol with its alpha adrenergic properties may increase coronary blood

flow while at the same time reduce myocardial oxygen demands in man.

Labetalol may also have applicability in situations where other beta adrenergic blocking drugs are contraindicated. Alpha adrenergic hypersensitivity has been shown to be important in many cases of bronchial asthma suggesting that the alpha adrenergic blocking activity of labetalol may be beneficial.<sup>22</sup> In asthmatic patients with angina pectoris Skinner and associates<sup>4</sup> found that propranolol administered intravenously produced bronchoconstriction in asthmatic subjects. Labetalol in equivalent cardiac beta adrenoceptor blocking doses did not cause bronchoconstriction. Labetalol also lowers peripheral vascular resistance in contrast to other beta adrenergic blockers that elevate resistance.<sup>23</sup> With its afterload reducing effects labetalol may be an ideal drug for patients with angina pectoris and hypertension associated with occult or mild congestive heart failure.

**Conclusions** In this pilot study labetalol was found to be a safe and effective agent for reducing spontaneous attacks of angina pectoris improving exercise tolerance and reducing high blood pressure. However, there are still many unanswered questions. Double blind studies need to be initiated in patients with angina pectoris comparing labetalol to other beta adrenergic blocking agents nitrates and placebo. The effects of labetalol on left ventricular function platelets and coronary blood flow in humans need to be elucidated. The effects of labetalol in normotensive patients with angina pectoris also must be examined.

Labetalol is an important pharmacological advance that provides an entirely new concept in management of patients with angina pectoris and hypertension—alpha beta adrenergic blockade.

### Summary

The safety and efficacy of oral labetalol an alpha beta adrenergic blocking drug was assessed in six patients with both angina pectoris and essential hypertension. Patients received a placebo for 3 weeks which was followed by a 4 week titration of labetalol (100 to 400 mg three times a day). The dose was then withdrawn over a 2 day period. With maximum doses of labetalol exercise tolerance as measured by multistage treadmill testing increased significantly com-

pared to placebo ( $p < 0.02$ ). At each exercise level (stage) the heart rate, systolic blood pressure and rate pressure product were reduced with labetalol treatment. There was no inhibition of exercise induced increases in heart rate. However, significant inhibition of the systolic pressure increment was seen at Stage II ( $p < 0.05$ ). While peak heart rate was not significantly different from baseline, the peak systolic blood pressure and rate pressure product were significantly reduced ( $p < 0.02$ ). Labetalol treatment significantly reduced the number of weekly spontaneous angina attacks ( $p < 0.05$ ). The resting supine and standing systolic and diastolic blood pressure were significantly reduced by labetalol ( $p < 0.01$ ). There was no significant reduction in the standing heart rate, but the supine heart rate was significantly reduced ( $p < 0.005$ ). There were no rebound hyperadrenergic effects following labetalol withdrawal. When used alone in patients with both angina pectoris and systemic hypertension, oral labetalol is a safe and effective drug for reducing the symptoms of angina pectoris, improving exercise tolerance and lowering high blood pressure.

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# Annotations

## Coronaviruses in Balkan nephritis

Viruses found in the kidneys were for a long time considered trivial symbionts, a viral flora. Only recently has it been recognized that these viruses might be subtle pathogens, possibly involved in slow initiation of progressive renal failure. Electron microscopic studies have revealed the presence of virus like particles in the kidneys of Balkan nephritis (BN) patients,<sup>1</sup> suggesting the implication of coronaviruses in renal pathology. However the presence of viruses in tissues does not alone establish causation. The involved virus could not be isolated as yet, but even the successful recovery of an agent from the kidneys would provide a very low order of evidence for the purpose of proving causality. In an earlier paper we described our program of work on the possible viral etiology of BN and presented negative results on attempts at virus isolation and identification of antibody reactivity to selected viral antigens. Because of the suggestion that BN in man might be caused by a slow porcine coronavirus infection this second progress report of our results is in order.

In the absence of virus isolations emphasis has been placed on seroepidemiological investigations. Antibodies have been measured by complement binding hemagglutination inhibition and by single radial hemolysis in gel in serum specimens of 34 BN patients, their relatives sharing their housing and living conditions and of 67 controls matched for age and sex. Sera from 21 pigs kept by patients were also examined. All sera were heat inactivated before testing. Antigens used in this survey were prepared in our laboratory with human, avian and porcine strains of coronavirus. The prevalence of antibodies to pig coronavirus was tested with the hemagglutinating encephalomyelitis virus 2063/68 strain. This strain was originally isolated from piglets with vomiting and wasting disease and it is closely related to if not identical with the hemagglutinating encephalomyelitis virus of swine and also related antigenically to the transmissible gastroenteritis virus of pigs.

None of the pigs from which serum was taken had either vomiting and wasting disease, transmissible gastroenteritis, infantile pyloric stenosis or encephalitis. Antibodies to the 2063/68 virus strain were found in serum from only one animal at a titer of 40. Human sera, whether of BN patients or of controls, yielded constantly negative results with this virus. Further investigations with the use of the OC 43 and the 229E strain of human coronavirus, and of the Beaudette and the Massachusetts 41 strain of avian infectious bronchitis virus revealed so far no statistically significant differences of the incidence of antibodies, the geometrical mean titer or the frequency of elevated titers between BN and control sera.

These findings must be interpreted with caution because of

the antigenic diversity of coronaviruses, of the lack of antigens for strains having fastidious growth requirements and because of the necessity to perform different assay procedures according to the various antigens used. The complement fixation reaction seems rather unsuitable for serosurveys, since complement fixing antibodies are relatively short lived. Neutralization is effective but expensive, slow and tedious while the hemagglutination inhibition test is impracticable with non hemagglutinating coronavirus strains. Moreover in a chronic viral infection there is always the possibility that antibody production may be masked by complete absorption of circulating antibody by excess antigen. It has to be remembered that the immunofluorescence test actually disclosed in the kidneys of BN patients a granular fluorescence along the basement membrane of the glomeruli, but the nature of the deposited immune complexes has not been investigated.

Coronaviruses are emerging as important causes of common cold like illness and are assumed to be involved in non bacterial gastroenteritis in humans. Lately their possible role in chronic renal disease has also been suggested. Understanding of the behavior and role of these viruses has been hampered greatly by the difficulties in propagation encountered in the laboratory. If the agent involved in the etiology of BN is an animal RNA virus, then it would account for the predominant rural distribution of the disease. Our results indicate that the examined BN patients have had no contact with porcine coronaviruses and they have experienced infections with human and avian coronavirus strains in the same manner and at a rate similar to that found in the control group. It appears therefore that the virus-like particles found in renal tubular epithelial cells of BN patients are of an antigenically unrelated strain or a different type. The suspected natural locality of BN (involving for instance some rodent coronavirus) would explain the restricted geographical distribution of this disease and its dependence on ecological factors. Since the mouse brain grown strain OC 43 consistently fixes complement at low levels with antisera hyperimmune to various strains of mouse hepatitis virus, it seems unlikely that this virus would be involved either. Further search for corona and other RNA viruses of rodents in the endemic area, screening of human sera for antibodies to such strains, and studies to identify their role in BN seem indicated. At the present time the role of coronaviruses in BN remains uncertain.

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## Cigarette smoking and coronary heart disease new evidence and old reactions

Although there is little doubt that cigarette smoking is a causal factor in lung cancer and chronic obstructive lung disease, there has been less agreement about the causal nature of the often found relation between cigarette smoking and coronary heart disease (CHD) for the following reasons. The relation between smoking and CHD has not generally been strong—usually smokers have shown about a twofold excess incidence over non smokers, in contrast with the tenfold increase for lung cancer. Relatively weak associations are often attributable to some underlying characteristic. Thus it has been proposed that some constitutional or genetic factors are present in the smoker that both lead him or her to smoke and predispose to CHD. This counterhypothesis has had some distinguishing support going back at least to the noted statistician R A Fisher, who was primarily concerned with smoking and an analogous problem with the evidence concerning smoking and CHD, that the relationship is not found in all studies; for example in the seven country collaborative study and associates U S railroad workers showed a CHD relationship but using similar data all other studies in Finland the Netherlands, Italy, Germany, and Japan did not and these countries range in CHD incidence. Another troublesome finding is smoking tends to be a weaker predictor of CHD in persons than in young and middle aged adults. This is the first of the factors for it does not seem to hold notion that smoking acts as a precipitating acute event in a fatal CHD largely and sudden cardiac death CHD with advanced atherosclerosis should be especially characteristic.

Then again the mechanism by which smoking promotes CHD has not been well established although vascular damage from carbon monoxide deleterious effects of increased catecholamine release and promotion of thrombotic tendencies have been proposed. Finally, data from studies of smoking discordant identical twins where the smokers and nonsmokers are genetically the same have not shown the degree of association between smoking and CHD as has been found in the general population where there is obviously no such genetic matching. Nevertheless because of small numbers of subjects, the twin data to date are too meager to be conclusive in this regard and a number of methodologic questions have been raised about these studies. Similar considerations apply to the association of smoking with total mortality of which deaths from CHD (but not from lung cancer or bronchitis) constitute a major component.

Probably the only study design that would convince virtually everyone that cigarette smoking itself does contribute to CHD would be a large scale controlled experiment in which young healthy persons were randomly assigned to smoke or not and in which they obeyed their assignment and were followed up over most of their lifetimes for CHD development. Such a study would be unethical and impossible to carry out. Therefore we must do the best we can with observational rather than experimental studies.

We recently published an observational study of the relationship of cigarette smoking to total and CHD mortality that took advantage of a large body of data that was collected on 4000 middle aged cigarette smokers examined here and non smokers who responded to periodic urging to take multiple health checkups. Because of the recruitment effect it

the degree of non response 17 per cent was relatively small for this type of study. More important the checkups provided a rich source of computer stored data that could be used to test a variety of reasonable alternatives to cigarette smoking itself as the explanation for the higher death rates in smokers observed during an 11 year follow up period. Thus we considered not only age sex race and other established CHD risk factors but also educational level alcohol use marital status presence of serious disease exposure to a variety of occupational hazards and medicinal drugs, and questionnaire responses suggesting depression and other emotional problems. Neither individually nor in combination did the 49 characteristics considered explain the association. After adjustment for these variables the smokers' total death rate was still 1.1 times higher than that of non smokers and the adjusted smoker/non smoker ratio for CHD death was 3.6.

I hope that this type of study can be repeated by others with extensive baseline information and follow up data available on smokers and non smokers. If more evidence against alternative explanations is accumulated the case for the responsibility of smoking itself will be further strengthened. On the other hand it is still possible (though unlikely in my opinion) for the counterhypothesis to be confirmed. Or perhaps smoking fosters the development of CHD in some persons and not in others. Additional data about pathogenesis should help explain the inconsistencies in the smoking-CHD evidence.

It would be best if such studies can be carried out in a spirit of scientific inquiry rather than in an attempt to prove that cigarettes do or do not cause CHD. Considerable suspicion is raised and emotional reactions are generated when one tries to perform objective research about controversial habits such as smoking or alcohol use. In the extreme publicity of our study by the media much was made of the fact that the financial support came from the tobacco industry. (Actually the grant was from the Council for Tobacco Research U.S.A. which is supported by tobacco companies but whose decisions as to what research to support are made by a group of distinguished physicians and scientists serving on its scientific advisory board. There were no requirements or "strings" attached to the grant and we felt no pressure from this granting agency to report or publish only findings favorable to smoking.) Thus our report which would be interpreted as unfavorable to cigarette smoking was considered credible because of its ultimate financial support by the tobacco industry. If the study had turned out differently and revealed some characteristics that explained away the smoking-mortality relationship many would not have believed the result and we would have been accused of being bought and paid for by the tobacco industry. Such an accusation was made by a reviewer for a different journal when we submitted a paper that raised questions about the comparability of persistent smokers and ex smokers with respect to CHD risk status determined at a time when all were still smoking.

We have had similar experiences in studying the relation of alcohol to cardiovascular disease. About one year ago a well known syndicated newspaper columnist raised questions about our credibility in this area since our study was funded in part by a grant from the U.S. Brewers Association, another organization whose research funding decisions are made by distinguished physicians and scientists with no attempt to influence the reports of grantees. The columnist had failed to note that our observation of a negative relation between

alcohol consumption and risk of myocardial infarction suggested the possibility of a protective effect was made under a research contract funded by the U.S. Government. (That we should suggest such a possibility also led to angry letters and comments at meetings by persons who obviously did not want to hear anything favorable about alcohol.) Ironically, our observation that alcohol use is correlated with elevated blood pressure, a possible detrimental effect, was from the study supported by the U.S. Brewers Association.

There are no easy solutions to the suspicion of bias raised by the source of financial support. It has been suggested that a researcher should accept no funding from an interested industry. Yet this is an important and valuable source of support in these times of tight money. Interposing an advisory committee between industry and an investigator may help but some critics will assume that the advisory committee has also been bribed. It must also be recognized that many skeptics believe that the government voluntary health agencies and various foundations have their own axes to grind and favor research that supports their interests and programs. So suspicion can thus be raised about studies supported by any source. Ultimately we must all rely on the integrity and objectivity of the researcher and the basic scientific process of repetition of studies by other investigators.

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## Coronary care—the limits?

Anyone who has practiced medicine in a hospital environment in the last 20 years will recall the helplessness of the cardiac arrest situation and contrast this with the efficient handling of that same occurrence in Coronary Care Units. This improvement developed logically from the recognition that the common cause of death after myocardial infarction ventricular fibrillation can be reversed electrically and that these patients subsequently do relatively well. These units appeared to halve hospital mortality rates, and in the United Kingdom many District General Hospitals have such units usually supervised by a team of general physicians, many of whom have interests outside cardiology. Are these developments justified in the light of more recent data?

Few would dispute that general physicians run efficient units or that if they are necessary these units should be situated in the District General Hospital setting. This is where most hospital medicine is practiced and where most patients who have sustained a myocardial infarction will receive care. Recent figures indicate no significant difference between ward and Coronary Care Unit mortality rates, and this together with the suggestion that some antidysrhythmic drugs are effective prophylactically suggests that the concept of the Coronary Care Unit requires reappraisal. These observations are invalid however because wards have benefited by the dissemination of equipment and expertise from Coronary Care Units. This is important as a feature of CCU is the manner in which they have crystallized the approach to the coronary patient and disciplined those responsible for it—medical and nursing staff. The contribution of the latter has been particularly valuable and is another example of the way in which the underrated potential of the nurse has been channelled to advantage. It would indeed be surprising if the impact of a CCU was not felt throughout a hospital and if ward mortality rates have fallen it is an argument for maintaining the CCU and not for removing it. Moreover there is no good evidence that antidysrhythmic therapy is of prophylactic value. There is certainly a need to design and staff CCU as less expensively remembering that their cost must be considered against that of the alternative—monitoring and nursing patients scattered throughout a department.

The problem with CCU is that their impact on mortality rate after MI is limited by the fact that 40 to 75% of deaths occur within the first hour. Patients are rarely admitted as quickly as this. Indeed 67% of deaths occur outside the hospital hence the efforts to extend resuscitative facilities with mobile units (MCCU's). There is no doubt that with enthusiasm drive and resources these units can have a small but significant impact on mortality. Where resources are extensive and include efforts to alter public attitudes the results can be very rewarding as has been found in Seattle. In ordinary hands, however MCCU's have often been disappointing and workers in Nottingham suggest that hospital based domiciliary services called by family doctors to cases of suspected myocardial infarction are unlikely to make a contribution to the lowering of mortality. Once more this is due to delay in reaching the patient. Not surprisingly at an especially difficult time for competing priorities, there is discussion about implementing MCCU's as no encouragement to those respon-

sible for health services and consequently no resources. Certainly there is no prospect of launching into the type of activity established in Seattle in the United Kingdom.

Another approach to the management of these patients is based on the long tradition of family medicine in the United Kingdom. There are now three studies which indicate that certain patients with MI can be kept at home. Though there are weaknesses to all three studies together they suggest that home management is safe for patients who have already survived about four hours before coming under medical care. Such management is nonetheless inappropriate for those with cardiac complications such as dysrhythmias, associated medical disorders or unsuitable social circumstances. The Nottingham group excluded from their trial 74% of the cases they visited at home on these grounds. In addition 90 to 40% of patients are not at home when they are stricken. Clearly quite a sizeable proportion of patients with MI will always require hospital admission but it is likely that many patients are admitted to the hospital unnecessarily. There are also some family doctors who feel they should play a very important role where patients are seen within the first hour or two. Colling<sup>2</sup> advocates that the family doctor who is usually called first, should attend immediately at the slightest suspicion of a myocardial infarction and stay with his patient over the two hours or so from the onset of the attack. During this period he would reassure, provide efficient analgesia, monitor and treat dysrhythmias medically. An important aspect of early management is as little movement of the patient as possible. It remains to be shown whether it is more important to keep these patients still or get them to a defibrillator quickly. Deaths occurred during ambulance transfer in the Teesside survey but the experience of mobile units suggests that this is not a problem in patients adequately managed prior to transportation.

There are certain problems with this approach however. It is unlikely that the majority of family doctors are confident enough to cope in the manner advocated by Colling and the use of antidysrhythmic drugs in general practice is potentially hazardous. It is estimated that a family doctor with an average list will come across perhaps a handful of cardiac arrest situations per year with of course variable success, perhaps too small to motivate him. He would certainly provide insufficient experience. Though the speed with which a family doctor responds to a call can be improved, it must be emphasized that the main cause of delay is patient delay which is difficult though not impossible to change. Of more importance the family doctor service has had to organize itself in an atmosphere of increasing health demands and expectations in a way (including the use of an out-of-hours deputizing service) which leaves little room for a rapid response to all potential coronary incidents and even less for the continuing time-consuming management in the home which is advocated. Additional time would also have to be found for the necessary training program. Nonetheless the message of intensive involvement by the family doctor as early as possible in the management of patients with MI should be encouraged but must include a defibrillator as the prime piece of resuscitative equipment. Access to this should not be a

problem since there is no reason why groups of family doctors should not organize their routine around this equipment as some have already done. This does require that family doctors think outside the limits of their own practices. Whether a doctor should extend his initial primary resuscitative role with continuing home management is an open question. Most doctors will not have the time for this and additionally it seems illogical to deprive a patient of a defibrillator after about two hours from the onset of the attack. Transfer to a CCU preferably using the services of an MCCU would seem more prudent. This faster tempo in the management of the infarct situation would make the case for the latter stronger.

In summary recent community studies suggest that a group of patients can probably be kept safely at home after a myocardial infarction. These results have been interpreted by some as a prescription for leaving all such patients at home. There is no evidence to support this and such an approach tends to remove the aura of urgency from what is a very urgent situation. The main objective must still be to get a defibrillator to the patient within two hours of the incident. Though there will always be exceptions which must be encouraged it would seem that in general the CCU and MCCU have reached the limit of what they can achieve towards this goal. It seems important therefore to encourage the call by certain family doctors for a leading role in primary resuscitation after myocardial infarction and this clearly is an area with a potential to affect mortality rates which has not been fully explored. The difficulties of this particular approach are not insuperable but only time will tell if family doctors are able to respond and if their response is worth while.

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## Of bibliographies

In recent years the references listed in the bibliographies of reports in medicine make readers wonder what is the purpose of a bibliography. It would seem that the purpose of a bibliography should be to orient, in proper perspective and time, the study being reported with related studies previously reported by others. Certainly a bibliography is not to be employed as a vehicle to indicate or suggest that the study being reported is partly or entirely new when it isn't. Nor is it proper to select references so as to imply that other authors

originally described or discovered a phenomenon in medicine or science when they didn't. Nepotism certainly is not to be accepted or condoned in science. Editors and reviewers are unable to evaluate bibliographies of all reports satisfactorily. The quality and accuracy of a bibliography reflects the quality and accuracy of the data of the study and the interpretation of the data. When the bibliography is inaccurate then how reliable are the data of the study and the reported interpretations? Readers are regularly impressed

with the failure of current reports to consider reports of the same type of study with similar results from the remote past. It would appear that authors tend to depend entirely on the references available through such services as Medline which catalogues publications of only the past 5 years or so. A thorough complete and careful review of the medical literature on any subject is an ordeal which is difficult and time-consuming but which is extremely informative educationally and proper. After all reports regardless of when they were published are there for critical scientists and physicians to observe and evaluate. Surely a thorough review of the literature would frequently reveal that a study similar to the one being reported had been reported many years earlier. This would improve the quality and reliability of reports and certainly would orient them in their proper temporal perspective. Few studies and findings are entirely new. A careful

review of the entire literature will reveal the importance of a study and whether or not it presents anything new as well as the need if any for its publication. Nepotism in publication is an error which reflects extremely unfavorably on the author. The bibliography and the use of references reflect the quality and accuracy of the data and surely the character of the author or authors and the total value and importance of a report. An inaccurate or inadequate bibliography certainly reflects an inaccurate and inadequate report. The bibliography is a part of the report. What is important is how the bibliography is used by the author.

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# Letters to the Editor

## Bradyarrhythmia after digitalis—chronic cardiotoxicity?

### To the Editor

I enjoyed your Annotation on digoxin-diuretic cardiomyopathy and I completely agree with your statement that "it is not possible to digitalize a patient properly with the use of digoxin."

Concerning the digoxin cardiomyopathy I would like to draw attention to the bradyarrhythmia which follows long term treatment with digitalis: it is possible that this bradyarrhythmia persisting in many subjects even after withdrawal of the drug may be the consequence of a chronic cardiotoxicity (delayed conduction at the level of A-V node?).

The digitalis cardiac glycosides have some similarities to daunorubicin and adriamycin.

The pathogenesis of anthracycline induced cardiomyopathy could be related to an intracellular overloading with calcium.

As with daunorubicin and adriamycin the inhibition by digitalis compounds of membrane NA-K-ATPase increases the intracellular calcium concentration.

One can therefore argue that this irreversible bradycardia which follows long term treatment with digitalis may result from permanent pharmacologic cardiomyopathy frequently unrecognized and mistreated.

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## Proficiency and cost effectiveness in pediatric hospitals

### To the Editor

This letter is written in response to the editorial entitled "The cost and benefits of segregation (by age)" by Dr Warren G Guntheroth which appeared in the May 1979 issue of the *AMERICAN HEART JOURNAL* (97:549 1979). In this editorial Dr Guntheroth suggests that The Guidelines for Pediatric Cardiology Diagnostic and Treatment Centers (Pediatrics 63:258-261) were written with a bias for pediatric hospitals.

The document that Dr Guntheroth refers to as Standards for pediatric cardiology diagnostic and treatment centers is in fact a Guidelines document. It in no way addresses the effectiveness of children's hospitals versus general hospitals, for the greater good of pediatric care.

The document does address the importance of performing a minimal number of pediatric procedures in order to maintain proficiency in any unit. It suggests that if children are to have cardiac catheterization or heart surgery a minimal number would need to be carried out in order to attain and maintain minimal proficiency and a degree of cost efficiency. Some children's hospitals and some general hospitals have performed large numbers of cardiac catheterizations and surgical procedures in children and these have been the institutions pioneering many procedures which are now considered the ultimate ways of caring for children. They have also trained some of the most respected pediatric cardiologists. Other children's hospitals and many general hospitals are caring for few infants and children with heart disease and thus, cannot maintain adequate proficiency of physicians, nurses and paramedical personnel. In addition units admitting few patients cannot afford to develop specialized facilities such as pediatric cardiac catheterization laboratories, intensive care units, and ward facilities which meet the special needs of infants, children and adolescents. It is for this reason that the guidelines suggest that the same minimal number of infants and children be cared for in either a children's hospital or in a general hospital.

The coordination of training of adult and pediatric cardiologists can occur in general hospitals handling children and adults or between children's hospitals and general hospitals where the good will of both the departments of internal medicine and pediatrics foster such behavior.

All of the members of the Standards Committee have spent their professional careers in general hospitals with pediatric units. To imply that the committee has developed self-serving standards to perpetuate children's hospitals is a misreading of the content and intent of the guidelines.

Standards Committee  
Section of Pediatric Cardiology  
American Academy of Pediatrics  
Arno Hohn  
Ira Gessner  
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### Reply

#### To the Editor

I appreciate the response of the Standards Committee to my Editorial, and knowing these Gentlemen well, I apologize for any implications that they personally were self-serving. On the other hand, I believe that an impartial reading of their "guidelines" will reveal at least a modest amount of "territo-



**Table 1** Mean standard oxygen dissociation curve ( $n = 9$ ) for human coronary sinus blood before and after nitroglycerin (NTG) (pH 7.4 pCO<sub>2</sub> 40 mm Hg T 37° C)

Saturation SO <sub>2</sub> %	(A) PO <sub>2</sub> mm Hg (+SD) before NTG	(B) PO <sub>2</sub> mm Hg (+SD) 5 min after NTG	(A)/(B)
5	5.4 (0.1)	5.6 (0.8)	-0.9
10	8.9 (1.0)	9.0 (0.7)	-0.1
20	14.1 (0.9)	14.1 (0.9)	-
30	18.2 (1.0)	18.1 (1.0)	+0.1
40	22.1 (1.2)	22.0 (1.2)	-0.1
50	26.1 (1.2)	26.0 (1.4)	+0.1
60	30.6 (1.4)	30.5 (1.7)	+0.1
70	36.2 (1.5)	36.1 (2.0)	+0.1
80	43.9 (1.7)	43.9 (2.5)	-
90	59.1 (2.5)	59.3 (4.0)	-0.9
95	79.0 (4.8)	79.8 (8.9)	-0.8
96	87.8 (5.3)	89.6 (8.9)	-1.8
97	9.9 (7.9)	106.1 (23.9)	-8.2
Hb g %	15.3 (1.0)	15.3 (1.0)	-
HbCO %	2.5 (1.0)	2.5 (1.0)	-
2,3 DPG ( $\frac{\mu\text{mole}}{\text{g Hb}}$ )	13.4 (2.4)	13.9 (2.1)	-0.5
Hct %	43.3 (2.7)	43.4 (2.7)	-0.1
MCHC %	35.3 (1.9)	35.3 (1.9)	-
$\Delta$ vol %	6.6 (0.7)	5.6 (0.7)	-

Age = 51 ( $\pm 9$ ) Smokers = 6 T test for paired data before and after NTG = NS + + +

Hb = hemoglobin HbCO = carboxyhemoglobin 2,3 DPG = diphosphoglycerate Hct = hematocrit MCHC = mean corpuscular hemoglobin concentration  $\Delta$  vol % = standard arteriovenous difference calculated in vol % between 80 and 35 mm Hg Po

imperative I am sure that we have no quarrel about the need for cost-effectiveness and good patient care particularly in a field where mistakes are apt to be fatal Of particular importance in relation to cost effectiveness the Standards Committee required of free standing pediatric hospitals a utilization of only 50% of that generally regarded as minimal for a general hospital Their letter implies that their primary purpose was efficiency of personnel However the assumption that supporting personnel will maintain proficiency only if patients are under some arbitrary age limit is without factual basis Similarly their letter and guidelines imply that bigger is better without evidence Although costs will clearly rise on a unit basis below some minimum number mortality and morbidity should serve as a more objective measurement of any programs right to be certified than an arbitrary number of cases under a given age I am aware of a major pediatric center in the East with poor surgical results in spite of a large caseload which subsequently improved dramatically when a cardiovascular surgeon (not a pediatric surgeon) was recruited I also disagree with the Committee's suggestion that innovations are directly related to caseload

If mortality and morbidity were used as an ongoing basis for certification centers doing only a handful of procedures would probably be eliminated rather quickly and assuredly they would be eliminated on a cost accounting basis Optimal care cost-effectiveness and good training are reasonable goals which can be shared by the public and most physicians I must reassert that segregation of children into free standing hospitals

and segregation of cardiovascular training is not the best way

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### Nitroglycerin and oxyhemoglobin dissociation curve of human coronary sinus blood

#### To the Editor

It has been shown in isolated dog heart preparations that nitroglycerin (NTG) significantly increased coronary venous Po and P<sub>50</sub> the effect was observed three minutes after the start of the infusion The amount administered (2 to 20  $\mu\text{g}/\text{minute}$ ) resulted in a blood concentration which was within the therapeutic dose range obtained in man The authors gave no satisfactory explanation for this phenomenon

We decided to confirm whether this effect was present or not in human subjects We studied nine male patients aged between 36 and 64 years in whom cardiac catheterization and coronary arteriography were performed for evaluation of chest pain suggestive of coronary disease seven had coronary artery disease one had cardiomyopathy and one had a normal coronary arteriogram

Blood was sampled in the coronary sinus before and five minutes after the administration of 1 mg NTG given sublingually. The oxyhemoglobin dissociation curve (ODC) of the whole blood was determined at standard conditions (pH 7.4, temperature 37°C and  $P_{CO_2}$  40 mm Hg) with an apparatus constructed in this laboratory. Hemoglobin and carboxyhemoglobin were measured by the IL-CO oximeter 282 hematocrit by microcentrifugation and diphosphoglycerate (2,3 DPG) by an enzymatic method (Sigma kit).

The results are summarized in Table I. The data clearly demonstrate that 1 mg NTG given sublingually influences neither the slope nor the position of the whole ODC nor the level of the 2,3 DPG. As we have previously observed that this drug had no effect on the same indices measured in the arterial blood, it can be concluded at least for the concentration, the method of administration employed, and the type of patients investigated that NTG does not induce a rightward shift of the ODC and therefore does not enhance oxygen delivery to the heart muscle through this mechanism. The discrepancy between our data and those of Warltier and associates is perhaps to be attributed to species differences.

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# Book reviews

**Advances in Heart Disease Volume 2** By Dean T. Mason  
New York 1978 Grune & Stratton Inc 552 pages Price  
\$36.00

This issue on *Advances in Heart Disease* edited by Mason is concerned with eight topics: advances in echocardiography, nuclear cardiology, ambulatory electrocardiography, exercise testing, exercise training, and cardiac rehabilitation, evasive evaluation of cardiac function, special cardiovascular treatment, and special cardiovascular topics. The many contributors present selected aspects of these eight topics, most of which are confusing to the average physician who practices in the small towns and villages of the world. These presentations fail to review critically each of these topics to indicate its more precise role in the care of patients outside of the large medical centers and large urban hospitals. The well-trained clinicians of the small towns and rural areas of the world who treat most of the sick need to realize that they are not handicapped when they fail to have immediate access to these special procedures. These procedures should be available only when indicated but they are rarely if ever indicated, e.g., nuclear cardiology. Regardless of the opinion of this reviewer, the book does present in satisfactory fashion in one volume recent advances in these special fields for the reader who does not follow closely the cardiology literature. The clinician who reads these advances carefully and critically can determine for himself how well he employs these special and costly procedures and can also learn how well he practices cardiology with or without dependence on them.

**Cerebral Circulation and Stroke** By Lawrence C. McHenry, Jr.  
St. Louis, Mo 1978 Warren H. Green Inc 280 pages  
Price \$22.50

This is a practical, small, concise book on an important problem in medicine. The book includes chapters on history, anatomy, physiology, diagnosis, and management of stroke. The illustrations are good but not very clear. These could be improved. The book is highly recommended to all medical students, housestaff, and internists as well as to family physicians. The correlation of central nervous system anatomy with the arterial blood supply is a good feature of the book. Physicians with a busy schedule will find the book very good and useful.

**British Heart Journal: Prevention of Arrhythmias. Proceedings of a Symposium** Arranged by Professor D. G. Julian  
London 1978 British Medical Association 98 pages Price  
\$3.50

This supplement of the *British Heart Journal* consists of the papers presented at a symposium held at Newcastle upon Tyne during September 1977. The 98 pages include 14 presentations concerning conduction tissues, effect of cardiac denervation, ventricular arrest, catecholamine effects, surgical treatment of ventricular tachycardia, effects of electrophysiology action of antiarrhythmic drugs, management of ventricular fibrillation, and other arrhythmic problems in coronary artery disease and use of drugs in preventing sudden death. There is really nothing new in this publication. However, the supplement provides a single source of information of considerable interest to cardiologists. This is a good publication.

**Cardiomyopathy Associated with Systemic Myopathy: Genetic Defect of Actomyosin Influencing Muscular Structure and Function** By Franz Buchner, Shinzo Onishi, and

Akira Wada  
Baltimore 1978 Urban & Schwarzenberg Medical Publishers 99 pages Price \$18.50

This small book on cardiomyopathy is devoted to an excellent model for the study of myocardial and systemic myopathy. The II Osaka hamster with a genetic myopathy provides an extremely useful source of material for researchers. The authors describe very vividly the clinical and pathologic manifestations of Bajaz Myopathy. Surely these little hamsters are of considerable value to clinical and laboratory research. However, this reviewer cannot avoid being "touched with sympathy and pity for these hamsters as the clinical manifestations of the disease unfold. This book is worth reading by everyone: physicians, researchers, and laymen to learn how these unfortunate animals suffer and contribute their lives and genetic background to I hope benefit mankind. The clinical course of the disease is well described and the manifestations of congestive heart failure are clearly presented. Man already owes much to these little hamsters.

**The Sinus Node: Structure, Function, and Clinical Relevance** Edited by Felix I. M. Bonke  
The Hague, Netherlands 1978 Martinus Nijhoff 409 pages Price 105 guilders

This book contains the papers presented at a workshop in the Netherlands during July 1977. The many papers review thoroughly many aspects of the function of the sinus node. Interest in the normal pacemaker of the heart cannot be over-emphasized. Much of the discussions are well known to those who follow the medical literature closely, but this book collects in one volume a fairly extensive review of the SA node function and disturbances in function with disease and treatment. This is a good, clear source of important information.

**Modern Electrocardiography** Edited by Z. Antozzy  
Amsterdam, The Netherlands—Oxford 1978, Excerpta Medica 567 pages Price \$77.50

This book contains the proceedings of the Fourth International Congress on Electrocardiography held in Hungary in September 1977. The many papers are brief and reflect very well the opinions of the authors. This reviewer shall not attempt to indicate differences related to data presented such as that on page 407 where the term "primary" T wave change related to the ventricular gradient was reported in the literature prior to 1969. Yet the author indicated this term was first reported in 1969. Some presentations are so brief that only the well-informed electrocardiographer can understand adequately the implications. Unfortunately, symposia these days are not sufficiently critical of data presented. Those interested in experimental electrocardiography can find the present state of research and thinking in electrocardiography in this book. Clinicians in busy practice of medicine will find the book of some but limited use. There certainly is a need to evaluate extensively and critically the applications and limitations of many ECG procedures such as Holter monitoring, treadmill exercise, His bundle electrocardiographic recordings, etc. The performance of ECG recordings needs critical review also. The recordings in general use have very poor fidelity.

**Circulatory Diseases of the Limbs: A Primer** By David I. Abramson  
New York, 1978, Grune & Stratton Inc 367 pages  
Price \$19.00

Abramson has written a small, concise, and clear "primer" on circulatory diseases of the limbs. The author has devoted his medical career to peripheral vascular diseases and is

certainly capable of producing an authoritative book on the subject for clinicians. The book is intended for doctors. It is clinically oriented and is written so that physicians in practice without sophisticated apparatus can manage peripheral vascular diseases very well. The chapters on history taking and physical examination are clearly written for clinicians and obviously written by one without extensive clinical experience. The lack of attention to peripheral vascular diseases in recent years in spite of the magnitude of the problem reflects the value and need for this book. This is a good book for all physicians. Its value can be even more appreciated by those who are already in the field of peripheral vascular disease and especially by physicians well informed of the physiology, pharmacology and pathophysiology of the blood vessels and lymphatics.

**Mechanisms of Vasodilatation.** Edited by P. M. Vanhoutte Wilrijk and I. Leusen. Cent. Basel, Switzerland. 1978. \$

Karger Medical and Scientific Publishers. 307 pages. Price \$53.50.

This symposium on mechanisms of vasodilatation should interest all physicians, physiologists and pharmacologists. The many papers are concerned with intrinsic factors related to vascular smooth muscle relaxation: local and humoral events, vasodilator agents used in clinical practice, neurogenic vasodilatation and general remarks. The papers are short but succinct. Much of the material presented is quite old, indicating an increased need for greater interest and research in the peripheral circulation. The importance of vasodilatation and the behavior of vascular smooth muscle is obvious. The regulation of blood flow to the most vital organs of the body as well as to the lungs is dependent upon vascular smooth muscle. This is a good book.

## Books received

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**Medical Physics Vol. 1.** By A. C. Damask. New York, 1978. Academic Press Inc. 374 pages. Price \$26.00.

**Physiology of Membrane Disorders.** Edited by Thomas E. Andreoli, Joseph F. Hoffman and Darrell D. Fanestil. New York, 1978. Plenum Publishing Corp. 1122 pages. Price \$75.00.

**Geochemistry and the Environment Volume III.** The National Research Council. Washington, D. C., 1978. National Academy of Sciences. 200 pages.

**The American Way of Life Need Not be Hazardous to Your Health.** By John W. Farquhar, M.D. New York, 1978. W. W. Norton & Company. 190 pages. Price \$9.95.

# Announcements

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## Teaching Film on the Failing Heart

Eli Lilly and Company is pleased to announce the availability of a new medical teaching film "The Failing Heart: Role of Inotropic Agents in Its Management".

Produced in consultation with Dr. Joe Noble, MD, FACC, the 25 minute film explains the physiology of the normal and failing heart, the role of calcium at the intracellular level, and the role of inotropic agents in correcting the pathophysiology. The film is available on loan from the Lilly Educational Resources Library, 565 Fifth Avenue, New York, N.Y. 10017. For further information, including purchase, write Eli Lilly and Company, Box 100B, Indianapolis, Indiana 46206.

## Postgraduate Course on Heart Disease

The University of Arizona Health Sciences Center, Tucson, announces its annual postgraduate education course entitled "Clinical Recognition and Management of Heart Disease" to be held on March 27 through 29, 1980, in Tucson, Arizona. The course is sponsored by the American College of Physicians. Registration information can be obtained from the Registrar's Office of the American College of Physicians or contact Gordon A. Ewy, MD, Professor of Medicine, Course Director, University of Arizona Health Sciences Center, Tucson, Arizona 85724.

## The International Society and Federation of Cardiology (ISFC)

The International Society and Federation of Cardiology (ISFC) combines scientific teaching and research with further education. Its Scientific Board and the Public Education Committee are respectively in charge of these activities and collaborate closely. The Scientific Councils organize multinational research studies, teaching seminars, and postgraduate courses and also set up task forces on proposed international classifications and definitions of arrhythmias, ischemic heart disease, cardiomyopathies, and hemodynamics. Important new developments in cardiology are also the target of special committees. The Public Education Committee attempts to educate the public in matters of preventive medicine and holds workshops and conferences. Hypertension was covered in 1979 and plans for additional workshops for 1980 to emphasize the cardiovascular dangers of cigarette smoking are being made. Another major function of the ISFC is to sponsor the World Congresses of Cardiology which are held every four years. The ISFC carries out its program in close liaison with the World Health Organization.

Further information may be obtained from the ISFC, P.O. Box 117, 1211 Geneva 12, Switzerland.

## Editorial

### Duplicity in a Committee Report on Diet and Coronary Heart Disease

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The advice of scientific committeemen frequently arrived at by consensus has profoundly influenced the dietary habits of Americans over the past 20 years. The validity of such advice needs examination from time to time.

The fourth report of the American Heart Association Committee on Nutrition appeared in the October 1978 issue of *Circulation*. It is worth while to test this report for its logic, epistemology, and philosophy by an unbiased research of the cited references. The Committee has stated

using standard methods for diet and coronary disease assessment, no population habitual in subsisting on a low fat and cholesterol diet or one that is low in saturated fats and cholesterol has an appreciable amount of coronary disease.

By extrapolation they suggest a diet high in saturated fat and/or cholesterol is an important factor for a high incidence of coronary heart disease.

This inference is not logical; it is specious. To establish a causal relationship, it must be shown that all population groups with high saturated fat and cholesterol intake also exhibit a high incidence of atherosclerosis. This is decidedly not the case with the French, the Eskimos, and the Masai, all populations consuming diets high in saturated fat.

Further, the so-called standard method for diet assessment are notoriously inaccurate and a reliable method for assessing coronary disease morbidity in large population groups is nonexistent. As for mortality, the gross inaccuracies arising from the use of death certificate data for cardiovascular-renal diseases are well known.

The high saturated fat consumption of the French people and their relatively low incidence of atherosclerosis have been noted by Keys and Keys, who attempted to forestall negative criticism of their study by stating that French physicians underdiagnose coronary heart disease.

The three allegedly favorable results of the early diet trials cited by the Committee do not provide sufficient evidence for any responsible scientist schooled in scrutinizing experimental data and reconciling them with public relations inspired propaganda. These trials were objectively analyzed by Davis and Havlik in Rifkind and Levis' *Hyperlipidemia: Diagnosis and Therapy*. They concluded the Los Angeles Veterans Administration Study failed to provide convincing proof of the lipid hypothesis. Analysis of the Finnish Diet Study data raised doubts about the validity and generalizability of the results. In the Oslo Diet-Heart Study, if total CHD mortality is considered including both fatal myocardial infarction and all sudden deaths combined, the results are not statistically significant.

Such critical and unbiased negative evaluations of these diet-heart studies differ

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from the positive assessments of the AHA Nutrition Committee and also from that of Hegsted in his most recent defense of the dietary goals which he helped prepare. The speciousness of the aforementioned trials for serum cholesterol lowering has been demonstrated. In objective science one expects to be shown not only positive findings but also negative results of legitimate trials. Such failures have been omitted from the report of the Nutrition Committee.

John S. Mill might have anticipated the so-called McGovern Report when he wrote in 1856:

Not the violent conflict between parts of the truth but the quiet suppression of half of it is the formidable evil. There is always hope when people are forced to listen to both sides. It is when they attend to only one that errors harden into prejudice and truth ceases to have the effect of truth.

The Minnesota Coronary Survey attempted to prevent CHD with a diet which consisted partially of 38 per cent fat with a polyunsaturated/saturated ratio of 1.6 and 166 mg of cholesterol. Of these 449 subjects the treated group did attain a 14 per cent decrease of serum cholesterol but during 4.5 years of total follow-up there were no significant differences in the number of myocardial infarctions, sudden deaths or strokes when all ages of men and women were combined. In men less than 50 years of age a favorable treatment effect was seen although the numbers were not large enough to achieve statistical significance. Yet according to Framingham Study statistics a 14 per cent reduction in serum cholesterol should have effected a 28 to 35 per cent decrease in CHD incidence.

With this critical examination of the cited positive evidence which is in reality negative one can only conclude that the Nutrition Committee has presented spurious claims of accomplishment to the uninitiated physician who may lack the time and training to evaluate the original findings for himself. The psychological motivation for the Committee's self-serving deception is not clear.

In a June 1978 article the same AHA Nutrition Committee admitted that there is no unequivocal scientific basis for the recommendation to lower serum cholesterol in the entire population and that it should be left to the judgment of the individual physician to advise

such a diet to his patients. A reasoned resolution of the controversy is not currently possible.

C. J. Glueck, a member of the Nutrition Committee, concluded in an article in *Drug Therapy* (October 1978) the same publication time as that of the Committee report. Since there is no unequivocal evidence regarding the effects and efficacy of dietary alteration in the most hypercholesterolemic group of children this question undoubtedly will remain controversial. The Committee is so inconsistent one doubts its validity.

Contrary to Dr. Glueck's downplaying of the potential for harm inherent in the dietary recommendations there is definite experimental and clinical suspicion that such an unnatural diet designed to lower serum cholesterol and consisting of up to 10 per cent polyunsaturated fatty acids (PUFA) may well have deleterious effects over time. In fact investigators at the University of Maryland have reported on carcinogenicity caused by trans unsaturated fatty acids contained in many margarine products.<sup>1</sup>

A much quoted authority on the alternate diet W. E. Connor has warned about PUFA:

Possible harmful effects of ingesting large amounts of polyunsaturated vegetable oils include enhanced formation of cholesterol gallstones, a stimulus to carcinogenesis, increased vitamin E requirements, promotion of obesity, increased uptake of plant sterols and possible increased cholesterol absorption. In a long term clinical trial the incidence of gallstones in autopsied individuals whose long term diet had contained a large amount of polyunsaturated fat was significantly increased over a control group. The threat of enhanced carcinogenesis still must be considered perhaps in part because of accumulation of peroxides or perhaps because a sudden increase in dietary polyunsaturated fat might provide an unusual stimulus for carcinogenesis.

Contrary to the statement of the AHA researchers that the Mediterranean diet is the same as their recommended one, I know of no

To gain representativeness and to attain the purpose of the present report, the 1978 American Medical Association Council on Food and Nutrition and the Food and Nutrition Board of the National Academy of Sciences' National Research Council restricted the dietary recommendation to individuals falling into the age group on the basis of their plasma lipids and did not extend the diet to the entire population starting in childhood as indicated by the AHA report.

population group which consumes fats in the proposed proportions of 10 per cent saturated 10 per cent monounsaturated and up to 10 percent polyunsaturated fatty acids Keys<sup>1</sup> reported a maximum consumption of only 7 percent polyunsaturated fatty acids which he extrapolated from his studies of very limited population groups in seven countries. However there are certainly many populations which consume saturated fats in amounts similar to that of North Americans but which have one third or less the CHD that is present in the United States. The lower prevalence of CHD in European population groups where all known risk factors are identical to those of North Americans has been reported by Keys. He is seeking the presence in Americans of another as yet undiscovered risk factor X.

One of the major completed trials the Coronary Drug Project was successful in lowering serum cholesterol but was an abysmal failure in its intended purpose—to demonstrate that a significant reduction of serum cholesterol will diminish the risk for recurrent myocardial infarction. However sometimes a dogma is so strongly entrenched that no disappointing adverse experimental results can dispel it. Wenger admitted without reservation in a paper delivered at the 1977 AHA meeting in Miami that the drugs employed in the Coronary Drug Project were without any beneficial effect. Still she has faith that appropriate diets in a healthy population would accomplish what the drugs had failed to do in a diseased group of CHD sufferers.<sup>2</sup> To quote the philosopher Sir Karl R. Popper: Every theory can be immunized against criticism. If we allow such immunization then every theory becomes unfalsifiable. What elevates science over pseudo science is the scientific method of finding true, secure and justifiable knowledge.

The 1978 AHA Committee Report mentioned for the first time the beneficial significance of cholesterol sequestered in high density lipoproteins (HDL). The three previous AHA statements dated 1965, revised 1968 and 1973 (not four as stated in the AHA Committee Report) made no note of this important finding. The prior committees were convinced of the completeness of their data but they forgot that the beneficial effects of HDL were reported as early as 1961. Which known facts have been overlooked in 1978 by the group of AHA

members forming the Nutrition Committee of this year?

I have tried to show that the evidence of undesirable high lipid levels of typical American men and women lies in the eyes of the beholder. Blackburn<sup>3</sup> has termed this condition 'mass hyperlipidemia'. This seems to be a newly invented epidemiological disease in search of a human body. The analogy of the benefit of reduction of elevated blood sugar in diabetic subjects which can be construed from studying the Nutrition Committee report cannot be applied to the reduction of allegedly elevated lipid levels in some atherosclerotic subjects until the minimum requirements of safety and efficacy of the recommendations have been proven. We should not be lured into dramatic action simply for the sake of *doing something* in the undeniable presence of a problem. Though they may sound very impressive, vague dietary recommendations have very little likelihood of curbing the epidemic of atherosclerotic diseases.

People have hailed what appears to be a substantial reduction of the cardiovascular disease death rate from a 1950 peak of 804.3 per hundred thousand for persons aged 55 to 64 to a low of 626 in 1973,<sup>4</sup> suggesting that the decrease was a natural consequence of eating the 'right kind of fats'.

Considering that the first AHA statement on fats was published in 1965 and granting a lead time of approximately 20 years from the inception of atherosclerosis to its clinical manifestation and eventual death, it is indeed difficult to attribute the drop in death rate to greater consumption of polyunsaturated vegetable oils.

To base recommendations for every American on untried, unproven, unsubstantiated data endangers not only the health of those Americans but also the future of medicine's credibility. We physicians, unlike the politicians, cannot afford the luxury of having a revised second edition in December 1977 of dietary goals which were thought to be the last word ten months before in February 1977. An editorial in *Lancet*<sup>5</sup> may serve as a warning against overstressing the significance of correlations and multiple regressions used as source material for the AHA report. Correlation and regression analysis of international differences in mortality against a wide variety of dietary, social and economic variables has a depressing history. It began with



and repeatedly turns to the enthusiastic interpretation of a few points purporting to represent the diets and coronary disease of millions of people of diverse backgrounds. The assertions of causality on the basis of such evidence have been at times extreme. But give a man three weapons—correlation, regression, and a pen—and he will use all three.

### Summary

The most recent American Heart Association Committee on Nutrition Report, *Diet and Coronary Heart Disease*, is examined for the applicability of its quoted references. It is concluded that the AHA advised diet, which includes 10 per cent saturated fats, 10 per cent monounsaturated fats, and up to 10 per cent polyunsaturated fats, should not be recommended for use by all Americans. There are serious unresolved questions concerning the expected benefits and the potential risks of such a glut of polyunsaturated oils for life-long use. There is no known large population group that consumes a diet up to 10 per cent of which is polyunsaturated oils.

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## R wave amplitude changes during stress testing Comparison with ST segment depression and angiographic correlation

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A reduction of R wave amplitude was found during exercise stress testing in normal subjects. In patients with coronary artery disease (CAD) an increase or no variations of R wave at all were observed.

Left ventricular volumes decrease in healthy subjects during exercise while in patients with CAD these volumes remain unchanged.

According to the observation of Brody, who postulated that the intracavitary blood mass affects the QRS amplitude, other authors have suggested that the exercise induced R wave amplitude changes may represent a useful index for detecting CAD.

In order to evaluate the usefulness of R wave amplitude changes ( $\Delta R$ ) in the screening of patients with CAD we compared the sensitivity, specificity and predictive accuracy of the  $\Delta R$  method with the standard ST segment depression and we tried to find a correlation between  $\Delta R$  and findings at coronary arteriography and left ventriculography.

### Materials and methods

Exercise stress tests records and coronary angiograms of 107 patients referred for evaluation of chest pain were reviewed retrospectively.

The patients were divided in the following groups. The normal group was composed of 100 subjects: 29 males and seven females, 34 to 60 years old, none of whom had coronary artery narrowing or abnormal left ventricular wall motion (0 V). The CAD group was composed of 71 patients with angiographic evidence of stenosis of 70% in one or more major coronary arteries.

These patients were divided into three groups. The first group was composed of 16 patients having one vessel disease (1 V); there were 12 males and four females between 33 and 61 years old. Four (25%) of these had electrocardiographic evidence of an old myocardial infarction, five (31%) of the 16 had an abnormal left ventricular contraction pattern.

The second group was composed of 31 patients having two vessel disease (2 V); there were 26 males and five females between 30 and 67 years old. Fourteen (45%) of these 31 had electrocardiographic evidence of an old myocardial infarction, 22 (71%) of the 31 demonstrated an abnormal left ventricular contraction pattern.

The third group consisted of 24 patients with three vessel disease (3 V); there were 22 males

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**Table I** True negative and false positive results using ST and  $\Delta R$  in 36 patients without angiographic evidence of CAD (zero vessel disease group  $N = 36$ )

	ST	$\Delta R$
TN	28 (78%)	19 (53%)
FP	8 (22%)	17 (47%)

$P < 0.05$  versus ST

TN = true negative FP = false positive

**Table II** Predictive accuracy sensitivity and specificity of  $\Delta R$  and ST standards

	$\Delta R$	ST
Predictive accuracy	78%	86%
Sensitivity	83%	75%
Specificity	53%	78%

$P < 0.05$

and 2 females with ages ranging from 42 to 71 years old. Fourteen (58%) of these showed electrocardiographic evidence of an old myocardial infarction and 20 (83%) of the 24 demonstrated angiographic evidence of abnormal left ventricular wall motion.

Patients underwent a progressive maximal exercise stress test using the maximal predicted heart rate as a target end point. Exercise testing was performed in a thermostatically controlled room (20°C) using a SASME Ergo 2 bicycle ergometer. All drugs were discontinued at least 48 hours before the exercise test. The patients started cycling in the sitting position with a 50 watt load which was increased by 20 watts every two minutes.

Exercise was stopped either because of chest pain or ST segment depression of 2 mm below the resting level. Electrocardiographic leads CM 4, 5 and II were monitored continuously (Aliconic 3000 model).

Significant ST segment depression was defined as 1 mm ST depression below the resting level 60 msec from the J point if the depression was horizontal or flat and 1.5 mm depression 80 msec from the J point if the depression was upsloping. The measurements of ST segment depression were made in the CM 5 lead in the immediate postexercise period.

Electrocardiographic recordings were obtained at rest every minute during exercise in the

**Table III** True positive and false negative results using ST and  $\Delta R$  in 71 CAD patients (CAD group  $n = 71$ )

	ST	$\Delta R$
TP	53 (75%)	59 (83%)
FN	18 (25%)	12 (17%)

TP = true positive FN = false negative

immediate postexercise period and every minute during the first 5 minutes of recovery.

R wave amplitude change was measured in millimeters from the isoelectric line to the peak of the R wave in CM 5 lead for at least 10 consecutive beats. The average value was used to minimize respiratory variations.  $\Delta R$  was measured comparing R wave amplitude at rest and immediately at the end of the exercise. As previously described, we considered  $\Delta R$  values equal or greater than zero to be significant for CAD Stress test records were evaluated in each group using ST segment depression and R wave amplitude changes.

Specificity, sensitivity and predictive accuracy for each method were calculated and compared. Statistical analysis was performed using the Fisher exact test.<sup>1</sup> Stress testing was evaluated without prior knowledge of the angiographic results.

Coronary angiograms were performed using the Sones technique<sup>1</sup> and were recorded on 35 mm film in multiple projections. Left ventriculography was performed in the right anterior oblique projection.

A luminal stenosis of one or more major coronary arteries equal to or greater than 70% was considered significant for CAD. The left ventricular angiograms were divided into five segments: (1) posterobasal, (2) diaphragmatic, (3) apical, (4) anterolateral and (5) anterobasal. Areas with an abnormal contraction pattern were described qualitatively as hypokinetic when systolic movement was less than normal, akinetic when no movement was observed during systole and dysketic when paradoxical systolic movement was seen. The angiograms were evaluated without prior knowledge of the stress test results.

The stress test results and angiographic record were examined by two independent observers.

Patients with cardiac valvular disease, cardiomyopathy, conduction defects, premature ventricular complexes or hypertensive cardiovascular

**Table IV** True positive and false negative results using ST and  $\Delta R$  criteria in one two and three coronary vessel disease patients

	ST		$\Delta R$	
	TP	FN	TP	FN
1 V (n = 16)	11 (69%)	5 (31%)	10 (63%)	6 (37%)
2 V (n = 31)	22 (71%)	9 (29%)	18 (58%)	4 (13%)
3 V (n = 24)	20 (83%)	4 (17%)	22 (92%)	2 (8%)

1 V = one vessel disease 2 V = two vessel disease 3 V = three vessel disease TP = true positive FN = false negative

lar disease and those taking digitalis or beta adrenergic blocking drugs were excluded

### Results

**Comparison between  $\Delta R$  and ST segment depression** Twenty eight (78%) of the 36 patients in the 0 V group had a true negative response during stress testing using the ST depression standard while only 19 (53%) of the 36 showed true negative results the using  $\Delta R$  method (Table 1). The specificity of the ST method was significantly ( $P < .02$ ) greater than  $\Delta R$  (Table II).

Fifty three patients (75%) of the 71 of the CAD group were true positives by the ST standard using  $\Delta R$  the true positive results increased to 59 patients (83%) however this increase of sensitivity was not statistically significant (Tables II and III).

The predictive accuracy of the two methods employed was similar (Table II).

As shown in Table IV both criteria produced similar results in patients with one vessel disease. However the  $\Delta R$  method showed better results in the 2 V and 3 V patients than ST segment depression.

**Correlation between  $\Delta R$  and angiographic findings** The R wave increased in seven (44%) of the 16 patients with one vessel disease it remained unchanged in three (19%) and decreased in six (37%) (Table V). Eleven patients of the 1 V group had normal left ventriculography  $\Delta R$  was equal to or greater than zero in six (54%) and was lower than zero in five (46%). In the five patients of the 1 V group with abnormal left ventricular wall motion  $\Delta R$  was equal to or greater than zero in four (80%) and lower than zero in one (20%) (Table V).

Twenty one patients (68%) of the 31 with two vessel disease had an increase of R wave ampli-

**Table V** Electrocardiographic results of stress testing in one vessel disease patients with abnormal and normal left ventricular wall motion using  $\Delta R$  criteria

	+ $\Delta R$	- $\Delta R$	+ $\Delta R$
1 V patients (n = 16)	7 (44%)	3 (19%)	6 (37%)
A.W.M (n = 5) (31%)	2 (40%)	2 (40%)	1 (20%)
N.W.M (n = 11) (69%)	5 (45%)	1 (9%)	5 (45%)

1 V = one vessel coronary disease A.W.M = abnormal left ventricular wall motion N.W.M = normal left ventricular wall motion

**Table VI** Electrocardiographic results of stress testing in two vessel coronary disease patients with abnormal and normal left ventricular wall motion using  $\Delta R$  criteria

	+ $\Delta R$	- $\Delta R$	+ $\Delta R$
2 V patients (n = 31)	21 (68%)	6 (19%)	4 (13%)
A.W.M (n = 22) (71%)	19 (86%)	2 (9%)	1 (5%)
N.W.M (n = 9) (29%)	2 (22%)	4 (44%)	3 (33%)

2 V = two vessel coronary disease A.W.M = abnormal left ventricular wall motion N.W.M = normal left ventricular wall motion

tude six patients (19%) had no change and four (13%) had a decrease (Table VI). Twenty two patients in the 2 V group demonstrated abnormal left ventricular wall motion 21 (95%) of these had  $\Delta R$  values equal to or greater than zero and only one (5%) showed  $\Delta R$  values lower than zero. Nine patients of the 31 of the 2 V group demonstrated a normal left ventriculographic pattern six (67%) of the nine had  $\Delta R$  values equal to or greater than zero while three (33%) showed  $\Delta R$  values lower than zero (Table VI).

Seventeen patients (71%) and five patients (21%) out of 24 of the 3 V group had an increase or no change of the  $\Delta R$  wave amplitude respectively only two (8%) of the 24 showed a decrease of the R wave (Table VII). Twenty patients of 24 in the 3 V group showed abnormal left ventricular wall motion 19 (95%) of the 20 had  $\Delta R$  values equal to or greater than zero while one (5%) showed a decreased R wave amplitude. Only four patients of the 24 of the 3 V group demonstrated normal left ventricular contraction pattern three (75%) of the four had  $\Delta R$  values greater than zero and one (25%) had a decreased R wave amplitude (Table VII).

The percentage of R wave abnormal results

**Table VII** Electrocardiographic results of stress testing in three vessel coronary disease patients with abnormal and normal left ventricular wall motion using  $\Delta R$  criteria

	$\Delta R$	$-\Delta R$	$\Delta R$
3 V patients (n = 24)	17 (71%)	5 (21%)	2 (8%)
A W M (n = 20) (83%)	14 (70%)	5 (25%)	1 (5%)
N W M (n = 4) (17%)	3 (75%)	—	1 (25%)

3 V = three vessel coronary disease A W M = abnormal left ventricular wall motion N W M = normal left ventricular wall motion

**Table VIII** Incidence of abnormal left ventricular wall motion in one, two, and three vessel coronary disease patients and of  $\Delta R$  values  $\geq 0$  in zero vessel subjects and in one, two, and three vessel coronary disease patients\*

	$\Delta R \geq 0$	A W M
0 V	19/36 (53%)	—
1 V	10/16 (63%)	5/16 (31%)
2 V	27/31 (87%)	22/31 (71%)†
3 V	22/24 (92%)‡	20/24 (83%)§

Statistical analysis performed by Fisher exact test

†P < 0.05 versus 1 V

‡P < 0.01 versus 1 V

§P < 0.001 versus 1 V

1 V = one vessel coronary disease 2 V = two vessel coronary disease 3 V = three vessel coronary disease 0 V = zero vessel coronary disease A W M = abnormal left ventricular wall motion

was significantly higher ( $P = 0.03$ ) in three vessel disease as compared with one vessel disease patients. There was no significant difference between the normal group and the single vessel disease group. The two vessel disease patients showed a higher percentage of  $\Delta R$  abnormal results as compared to the single vessel disease patients; this difference exhibited a borderline  $P$  value ( $P = 0.06$ ) (Table VIII).

In the 2 V and 3 V groups abnormal left ventricular wall motion was found more frequently than in the 1 V group ( $P < 0.01$  and  $P < 0.002$  respectively) (Table VIII).

## Discussion

Recent reports have suggested that exercise-induced R wave amplitude changes may be a useful index for detecting CAD. Bonoris and associates obtained these results in a population with a large number of false positive and negative responses using the ST segment depression method. However, we believe that such findings can be

influenced by the purposely introduced large number of false negative and false positive results.

Therefore, the purpose of our study is to establish if R wave amplitude changes can be used as a screening method for detecting patients with CAD when compared with more reliable ST segment depression results and also if the  $\Delta R$  standard can be related to the angiographic severity of CAD.

Increased sympathetic activity during stress testing is responsible for a reduction in left ventricular volumes in normal subjects.<sup>1</sup> Further reports have supported the evidence that the R wave amplitude is related to the left ventricular blood volume.<sup>2</sup> Therefore, the reduced QRS amplitude during an exercise stress test is likely to be related to the reduction of the left ventricular volume.

On the other hand, in patients with CAD the R wave amplitude increases or does not change at all; such findings are likely to be related to the left ventricular impairment during exercise in these patients.<sup>3</sup> Indeed, cardiac volume increases during atrial pacing or exercise-induced angina,<sup>4,5</sup> moreover myocardial ischemia causes or worsens left ventricular impairment.<sup>6,7</sup>

Our results are consistent with those of other authors who found a correlation between  $\Delta R$  values equal to or greater than zero during stress testing and the severity of CAD. The patients with single vessel disease showing the lowest incidence of abnormal left ventriculograms demonstrated the lowest percentage of  $\Delta R$  values equal to or greater than zero during the exercise stress test. The patients with double and triple vessel disease showing left ventricular contraction abnormalities very frequently demonstrated a  $\Delta R$  value equal to or greater than zero. Indeed, 92% of the patients in the 3 V group had an increased or unchanged R wave amplitude, the highest percentage recorded in our series. However, we must emphasize the limitations in the  $\Delta R$  evaluation of stress testing. As previously described by other authors, the ST segment depression is well correlated with CAD; the sensitivity of this method ranges from 80% to 55% and its specificity ranges from 80% to 90%.<sup>8-11</sup> Our results agree with these values. We found that the R wave method is more sensitive than ST segment depression, but the latter is significantly more specific than the former.

It has been reported that the false negative

results are more common in less severe CAD.<sup>3,11</sup> Our results show that the R wave amplitude changes as well as ST segment depression have a comparable incidence of false negative results in patients with single vessel disease.

Only 53% of the patients in the 0 V group have  $\Delta R$  lower than zero during stress testing; our results agree with those of Gillespie and colleagues<sup>31</sup> who demonstrated the high sensitivity but also the low specificity of the  $\Delta R$  method.

Other authors found abnormal R wave changes during stress testing in about 10% of young subjects without any clinical evidence of CAD and with a negative stress test using the ST method. The mechanism responsible for such an increase of the R wave amplitude in healthy subjects is unknown.

On the other hand R wave amplitude may decrease even in patients with CAD if the hypercontractility of the normal areas of myocardium counterbalances the effects of diseased areas. We believe that while such a mechanism could be effective in less severe CAD patterns it is unlikely to be effective in patients with severe CAD and left ventricular impairment bearing in mind that the left ventricular performance is further impaired during myocardial ischemia.<sup>3</sup>

These controversial results indicate that the analysis of the R wave changes during exercise stress testing might necessitate further research. To attribute them to the functional impairment is not entirely satisfactory. It is likely that the left ventricular impairment during exercise is a very important determinant but other factors could also play a role.

In conclusion it is true that the R wave amplitude often increases during stress testing in patients with CAD and this increase is very likely related to the more severe angiographic CAD pattern. Thus the  $\Delta R$  method improves the sensitivity of exercise stress testing; however this is accompanied by a concomitant reduced specificity. Therefore we consider that the usefulness of the  $\Delta R$  method remains to be determined.

### Summary

One hundred and seven exercise stress tests and coronary angiograms were reviewed retrospectively in order to evaluate the usefulness of R wave amplitude changes ( $\Delta R$ ) during exercise compared with ST segment depression in the screening of patients with coronary artery disease (CAD).

We also attempted to correlate  $\Delta R$  with the severity of CAD as expressed by coronary arteriography and left ventriculography.

Thirty six patients showed no coronary artery narrowing (0 V); the remaining 71 patients with stenosis of 70% of at least one of the major coronary arteries were divided into three groups.

Sixteen patients had single vessel disease (1 V) five (31%) in this group showed abnormal left ventricular wall motion. Thirty one patients had two vessel disease (2 V) 22 (71%) of the 31 demonstrated abnormal left ventricular wall motion. Twenty four patients had three vessel disease (3 V) 20 (83%) of the 24 showed abnormal left ventricular wall motion.

We considered  $\Delta R$  values  $\geq 0$  and ST segment depression  $\geq 1$  mm significant for diagnosis of CAD.

The sensitivity of the  $\Delta R$  method in predicting CAD was superior to the method based upon ST segment depression; however the latter was significantly ( $P < 0.02$ ) more specific than the former. The predictive accuracy of these two criteria was similar.

We found  $\Delta R$  values  $\geq 0$  more frequently in the 2 V and 3 V groups as compared with the 1 V group. Patients of the 2 V and 3 V groups had a significantly higher incidence of abnormal left ventricular wall motion ( $P < 0.01$ ,  $P < 0.0002$  respectively) in comparison with 1 V patients. Thus  $\Delta R$  values  $\geq 0$  during exercise stress testing are very likely related to left ventricular impairment.

Even though the accuracy of the  $\Delta R$  method was greater in more severe CAD it seems to be offset by a concomitant decrease in specificity.

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**Table VII** Electrocardiographic results of stress testing in three vessel coronary disease patients with abnormal and normal left ventricular wall motion using  $\Delta R$  criteria

	$\Delta R$	$-\Delta R$	$\Delta R$
3 V patients (n = 24)	17 (71%)	5 (21%)	2 (8%)
A W M (n = 20) (83%)	14 (70%)	5 (25%)	1 (5%)
N W M (n = 4) (17%)	3 (75%)	—	1 (25%)

3-V = three vessel coronary disease; A W M = abnormal left ventricular wall motion; N W M = normal left ventricular wall motion

**Table VIII** Incidence of abnormal left ventricular wall motion in one, two, and three vessel coronary disease patients and of  $\Delta R$  values  $\geq 0$  in zero vessel subjects and in one, two, and three vessel coronary disease patients\*

	$\Delta R \geq 0$	A W M
0 V	19/36 (53%)	—
1 V	10/16 (63%)	5/16 (31%)
2 V	27/31 (87%)	20/31 (71%)
3-V	22/24 (92%)	20/24 (83%)

\*Statistical analysis performed by Fisher exact test.

†P < .03 versus 1 V.

‡P < .01 versus 1 V.

§P < .005 versus 1 V.

1 V = one vessel coronary disease; 2 V = two vessel coronary disease; 3 V = three vessel coronary disease; 0 V = zero vessel coronary disease; A W M = abnormal left ventricular wall motion.

was significantly higher ( $P = .03$ ) in three vessel disease as compared with one vessel disease patients. There was no significant difference between the normal group and the single vessel disease group. The two vessel disease patients showed a higher percentage of  $\Delta R$  abnormal results as compared to the single vessel disease patients; this difference exhibited a borderline  $P$  value ( $P = .06$ ) (Table VIII).

In the 2 V and 3 V groups abnormal left ventricular wall motion was found more frequently than in the 1 V group ( $P < .01$  and  $P < .002$  respectively) (Table VIII).

## Discussion

Recent reports have suggested that exercise induced R wave amplitude changes may be a useful index for detecting CAD. Bonorris and associates obtained these results in a population with a large number of false positive and negative responses using the ST segment depression method. However, we believe that such findings can be

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Increased sympathetic activity during stress testing is responsible for a reduction in left ventricular volumes in normal subjects.<sup>1</sup> Further reports have supported the evidence that the R wave amplitude is related to the left ventricular blood volume.<sup>1</sup> Therefore, the reduced QRS amplitude during an exercise stress test is likely to be related to the reduction of the left ventricular volume.

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Our results are consistent with those of other authors who found a correlation between  $\Delta R$  values equal to or greater than zero during stress testing and the severity of CAD. The patients with single vessel disease showing the lowest incidence of abnormal left ventriculograms demonstrated the lowest percentage of  $\Delta R$  values equal to or greater than zero during the exercise stress test. The patients with double and triple vessel disease showing left ventricular contractive abnormalities very frequently demonstrated a  $\Delta R$  value equal to or greater than zero. Indeed, 92% of the patients in the 3 V group had an increased or unchanged R wave amplitude, the highest percentage recorded in our series. However, we must emphasize the limitations in the  $\Delta R$  evaluation of stress testing. As previously described by other authors, the ST segment depression is well correlated with CAD; the sensitivity of this method ranges from 80% to 55% and its specificity ranges from 80% to 90%.<sup>4,5</sup> Our results agree with these values. We found that the R wave method is more sensitive than ST segment depression but the latter is significantly more specific than the former.

It has been reported that the false negative

# The natural history of aortic stenosis in adults

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Information on the natural history of valvular aortic stenosis in adults is essential in their proper management. Previous studies of such cases diagnosed on clinical and postmortem findings suggest poor prognosis with the onset of angina, syncope and congestive heart failure. A subsequent study involving a small number of cases with hemodynamic confirmation tends to support this premise. Since aortic valve surgery developed simultaneously with cardiac catheterization techniques, most patients subsequently diagnosed as having significant aortic stenosis have been selected for valvuloplasty or valve replacement. Therefore, natural history data in aortic stenosis are based on a small number of hemodynamically studied patients and large series are unlikely to be reported in the future. The present study provides a unique opportunity for long term follow up of 42 adults with hemodynamic documentation of isolated valvular aortic stenosis.

## Methods

Forty two consecutive adults aged 20 years or older with isolated valvular aortic stenosis seen initially at Georgetown University Hospital

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between 1966 and 1971 were identified. All had hemodynamic confirmation of the diagnosis and for various reasons did not undergo early surgical intervention. Cases with associated moderate or severe aortic insufficiency or mitral valvular disease were excluded. Thirty two patients were symptomatic and ten were asymptomatic at the time of initial clinical assessment and cardiac catheterization. The hemodynamic severity of aortic stenosis was defined according to the following parameters:

1. Mild aortic stenosis: Aortic valve area (AVA) greater than 1.1 cm<sup>2</sup> and/or a systolic peak to peak gradient less than 40 mm Hg.

2. Moderate aortic stenosis: Aortic valve area (AVA) of 0.71 to 1.09 cm<sup>2</sup> and systolic peak to peak gradient of less than 70 mm Hg.

3. Severe aortic stenosis: Aortic valve area of 0.7 cm<sup>2</sup> or less and/or a systolic peak to peak gradient of greater than 70 mm Hg.

Patients in the moderate and severe categories both met previously described criteria for significant stenosis.<sup>1,2</sup> All patients had a history and physical examination by two or more members of the cardiology division. The precatheterization assessment included a phonocardiogram, cardiac series and a 12 lead electrocardiogram. Left ventricular hypertrophy (LVH) was identified according to the electrocardiographic criteria of Sokolow and Lyon. Aortic valve calcification was determined by chest x ray or fluoroscopy. A mortality curve for symptomatic patients with hemodynamically moderate or severe stenosis was constructed by regression analysis to obtain a line of best fit.<sup>3</sup>

## Results

**A Symptomatic aortic stenosis.** Thirty two patients were symptomatic at the time of cardiac



Table I Symptomatic moderate aortic stenosis

Pt	Age/sex	Mos from onset to cath			Peak to peak gradient (mm Hg)	LVEDP (mm Hg)	AVA (cm <sup>2</sup> )	Status (time from cath to follow up)
		Angina	Syncope	CHF				
GB	62 M	1	0	12	20	8	0.90	Died age 67 ( 2 months)
WB	55 M	0	0	12	34	—	0.90	Alive (76 months)
TF	61 M	36	0	12	54	24	—	Died age 61 ( 2 days)
BF	61 M	0	0	84	29	32	—	Died age 62 ( 1 month)
LH	46 M	0	6	12	47	10	0.80	AVR (64 months)
RR	60 M	96	0	0	71	15	0.90	AVR (33 months)
RZ	49 M	1	1	0	38	12	0.80	Died age 50 ( 8 months)
JS	52 M	0	2	2	41	3	1.13	Died age 53 (77 months)
EM	62 M	0	0	3	37	13	0.90	Died age 64 (77 months)
CH	22 M	0	0	60	37	8	0.80	Alive (80 months)

Table II Symptomatic severe aortic stenosis

Pt	Age/sex	Mos from onset to cath			Peak to peak gradient (mm Hg)	LVEDP (mm Hg)	AVA (cm <sup>2</sup> )	Status (time from cath to follow up)
		Angina	Syncope	CHF				
WB	56 M	0	0	12	150	24	0.3	Died age 56 ( 6 months)
FC	58 M	12	0	60	87	33	—	Alive ( 61 months)
CH	63 F	12	1	12	120	21	0.44	Died age 63 ( 3 days)
JJ	60 M	0	2	4	100	11	—	Died age 60 ( 9 days)
JL	72 M	0	12	0	60	31	0.50	Died age 69 ( 12 months)
JM	59 F	12	0	12	30	6	0.60	Alive (114 months)
CM	44 M	9	9	9	99	30	—	Died age 44 ( 2 weeks)
MM	64 F	6	6	6	98	18	0.40	Died age 64 ( 1 month)
DR	48 M	0	0	4	88	18	0.40	Died age 48 ( 3 months)
KR	53 F	0	0	6	88	40	0.20	Died age 53 ( 1 month)
JS	72 M	6	0	0	87	20	0.50	Died age 65 ( 33 months)
RZ	77 F	0	2	84	60	4	0.50	Died age 71 ( 2 months)
RF	40 M	24	24	24	80	18	0.90	AVR ( 3 months)

catheterization. Thirteen had severe, 10 had moderate, and nine had mild aortic stenosis. Patients in the moderate and severe groups are listed in Tables I and II with selected clinical, hemodynamic, and follow-up data. Survivors in these groups were followed from 26 to 114 months (average 64.4 months) from the time of catheterization.

Ten of the 13 patients with severe, six of the 10 with moderate, and four of the nine with mild stenosis were dead by the end of the follow-up period. Fig. 1 represents a mortality curve from the onset of the first symptom from those patients in the moderate and severe categories. Data points are corrected for the number of patients followed for each time period; e.g., only 17 of the 23 patients were followed for a total of 11 years. Twenty-six per cent were dead by one year after the first symptom, 48% by two years, 57% by

three years, 64% by five years, 80% by eight years, and 94% by eleven years.

Table III shows the prevalence and duration of symptoms for patients with moderate and severe aortic stenosis. Congestive heart failure was the most common symptom (83%). Although the average survival was shorter in patients with syncope, no symptom carried a significantly worse prognosis because of the wide variability in duration of survival. Symptoms of congestive heart failure, for example, were present in two patients (one with moderate, one with severe stenosis) for eight years before death. Among surviving patients, one with a gradient of 84 mm Hg and left ventricular end diastolic pressure (LVEDP) of 33 mm Hg had symptoms of congestive failure for over eight years.

Although the mortality rate was somewhat greater in patients with severe (77%) than in those

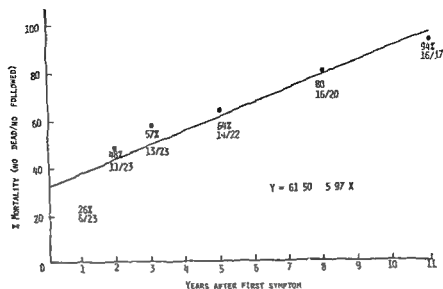


Fig 1 Mortality curve for symptomatic patients with moderate and severe aortic stenosis. A line of best fit is constructed by regression analysis.

Table III Duration of symptoms in patients with significant aortic stenosis

Symptom	No with symptom/ no of asymptomatic patients	No dead/no with symptom	Duration of Symptoms (months—onset to death)
Angina	11/23 (48%)	7/11 (64%)	3.39 Mean 16.43 ± SD 14.67 (SE 5.55)
Syncope	10/23 (44%)	8/10 (80%)	2.4 Mean 10 ± SD 9.13 (SE 3.23)
CHF	19/23 (83%)	13/19 (68%)	4.36 Mean 23.80 ± SD 28.11 (SE 7.80)

with moderate stenosis (60%) the difference was not significant. Survival within the moderate and severe groups was also plotted against peak to peak gradient, aortic valve area, and left ventricular end diastolic pressure. While patients with higher left ventricular end diastolic pressures had somewhat higher mortality rates, no significant differences were observed.

Of the 16 patients with moderate or severe aortic stenosis who died, eight died suddenly without reaching a hospital. Four died with progressive congestive failure, two died with myocardial infarction and cardiogenic shock (which occurred three days after catheterization in one patient). One patient reached the hospital in a comatose condition and in pulmonary edema after a syncopal episode. The mode of death is unknown in one patient.

Four of the ten patients in the mild category were dead by the end of the follow up period. All

four had histories of congestive heart failure and three had histories of angina.

**B Asymptomatic aortic stenosis** Eight patients (Table IV) in the moderate and severe groups were asymptomatic at the time of cardiac catheterization and three have not had subsequent aortic valve surgery. These patients have survived for periods ranging from 29 to 84 months (average 59.7 months) and remain asymptomatic. Of note, all these patients are less than 30 years old. The other five patients were asymptomatic at the time of catheterization but have subsequently had aortic valve replacement because of the onset of symptoms after surviving an average of 75.8 months (20 to 139 months). These patients also were less than 30 years old.

## Discussion

**Symptomatic aortic stenosis** It is a widely held clinical view that symptomatic hemody-

Table IV Asymptomatic patients with significant aortic stenosis

Patient	Age at Cath (yrs)	Category	Peak to peak gradient (mm Hg)	Follow up after cath (months)	Interval between cath & AVR (months)
RB	24	Severe	72	84	—
SC	22	Severe	59	—	139
WD	25	Moderate	58	29	—
RY	20	Moderate	50	66	—
LR	22	Moderate	53	—	78
NG	29	Severe	100	—	79
LK	29	Severe	75	—	20
RH	22	Moderate	64	—	114

namically significant aortic stenosis carries a poor prognosis.<sup>11-14</sup> The prognosis for the 23 symptomatic patients with moderate or severe stenosis in our study was somewhat worse than in those previously reported.<sup>15</sup> Forty-eight % were dead two years after the onset of the first symptom, 64% had died by five years, and 94% had died by eleven years (percentages are corrected for the number of patients followed). The worse prognosis in our study compared to that of Frank, Johnson, and Ross<sup>15</sup> may be explained by our exclusion for separate consideration of patients asymptomatic at the time of cardiac catheterization who appear to have a lower mortality rate.

Among those patients with symptomatic hemodynamically significant aortic stenosis no subgroup at higher risk could be identified. Although congestive heart failure was the most common symptom and syncope presaged the shortest average survival, no symptom carried a significantly worse prognosis. Patients with severe stenosis had a slightly worse but not significantly different prognosis than those in the moderate group with ten of 13 patients (77%) dead by the time of follow up versus six of ten dead (60%) in the moderate category. Higher left ventricular end diastolic pressure carried a slightly worse prognosis but did not clearly separate survivors from those who died.

It is striking that those patients classified as having mild aortic stenosis also demonstrated a very high mortality rate, with four of nine (44%) of these patients dead by the end of the follow up period. This result probably reflects the presence of associated myocardial disease of other etiology (one had a documented acute myocardial infarction and another had calcified coronary arteries) rather than the aortic valve lesion alone. Since coronary arteriograms were not performed on

these patients this conclusion is speculative. However, coronary artery disease associated with aortic valve disease in the older patient is common.<sup>11-17</sup> Its presence is not necessarily predictable by the presence or absence of angina pectoris.<sup>11-17</sup> In one large series 58% of those with significant aortic stenosis and angina pectoris had angiographically documented coronary artery disease, of those with aortic stenosis without angina 26% had coronary artery disease.<sup>18</sup>

Of the 16 patients in the moderate and severe groups who died, eight died within hours of manifesting new symptoms without reaching a hospital, and another died shortly after arrival in a hospital emergency ward in a comatose condition and with pulmonary edema after a syncope episode. All these patients were symptomatic before death. This result confirms the accepted frequency of sudden death in symptomatic aortic stenosis and represents a higher incidence than the 10 to 20% previously reported.<sup>11-13</sup>

Our data demonstrate that symptomatic hemodynamically severe or moderate aortic stenosis carries a very high mortality. Survival is significantly less than that reported in patients undergoing aortic valve replacement for aortic stenosis.<sup>11-13</sup> Surgery is therefore indicated for these patients.

**Asymptomatic aortic stenosis.** Patients with moderate or severe aortic stenosis who are without symptoms pose a special therapeutic problem to the clinician. One hesitates to subject an asymptomatic patient to a surgical intervention which carries a significant mortality rate.<sup>11-13</sup> However, there is always the concern that without surgery the patient is at risk of sudden death. Moreover, it can be argued that delaying surgery may lead to myocardial deterioration which could

increase operative mortality and compromise the long term results of aortic valve surgery

There are considerable data on the risk of sudden death in children with congenital aortic stenosis. This risk has been placed as high as four % per year for the first three decades<sup>23</sup> but the subgroups at risk can be identified with some assurance. It has been said that patients less than 20 years old with congenital aortic stenosis who die suddenly are symptomatic and/or demonstrate a left ventricular strain pattern by electrocardiogram and that the incidence of sudden death in a child without symptoms or a left ventricular strain pattern is almost nil. However the recent Joint Study on the Natural History of Congenital Heart Defects followed a large group of children—most of whom had mild aortic stenosis—and identified three patients who died suddenly all with significant aortic stenosis. One of these a 16 year old child did not demonstrate a left ventricular strain pattern. Therefore the absence of such a pattern cannot be considered a guarantee against the risk of sudden death.

The risk of sudden death in asymptomatic adults with hemodynamically significant aortic stenosis is less well established. It can certainly occur. One of three such patients (a 45 year old male) reported by Frank, Johnson and Ross died suddenly. In summarizing data from retrospective studies without hemodynamic confirmation, Ross and Braunwald state that only three to five percent of the deaths in acquired aortic stenosis appear to occur suddenly in patients without symptoms.<sup>24</sup> However these data are derived from patients dying suddenly and the authors assess the patients' symptomatic status retrospectively. They do not quantitate the risk of sudden death or the prognosis of the asymptomatic patient with significant aortic stenosis.

Eight of our patients with moderate or severe aortic stenosis were asymptomatic at the time of catheterization. These patients were not typical of the study population in that all were less than 30 years old when catheterized. All had murmurs detected in childhood and presumably had congenital aortic stenosis. Five of the eight had left ventricular strain by electrocardiogram. Of the eight patients, three subsequently developed symptoms (all three with congestive heart failure, angina in two) and underwent aortic valve replacement. Five are alive without surgery at the

end of the follow up period (four remaining asymptomatic). None of the eight asymptomatic patients therefore experienced sudden death in a follow up period averaging 69 months.

These data are of course limited both in the number and in the unrepresentative nature of the adult patients involved. However along with the studies previously cited they suggest that while sudden death can occur in asymptomatic adult patients with severe aortic stenosis it is uncommon and thus not a paramount indication for aortic valve surgery. Therefore the decision to replace the aortic valve in these patients depends on a clinical judgment weighing the small risk of sudden death before the development of symptoms (which clearly warrant surgery) against the morbidity and mortality of valve replacement and life with a prosthetic valve.

### Summary

Accepted clinical views about the natural history of aortic stenosis are based on surprisingly little hemodynamically documented data and further information is unlikely to be forthcoming in the modern surgical era. Therefore follow up data were obtained on 42 adult patients with isolated valvular aortic stenosis catheterized at Georgetown University Hospital who did not undergo early valve replacement.

Of 32 symptomatic patients 23 had moderate or severe stenosis and were followed until death or for an average of 64.4 months after catheterization. The prognosis was more ominous than previously reported. Mortality rates from onset of symptoms were 26% at one year, 48% at two years and 57% at three years. Fifty six % of deaths occurred suddenly; within hours of new symptoms.

Asymptomatic patients with moderate or severe stenosis did not share the high mortality rate of those with symptoms. Eight such patients were followed for an average of 69 months and none died.

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## ail aortic valve leaflets M-mode and two-dimensional echocardiographic manifestations

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udden disruption of aortic valve integrity results in acute severe aortic insufficiency (AI). The pathophysiology, clinical recognition and management of this life threatening syndrome has been thoroughly reviewed by Morganroth and associates. Flail ruptured and prolapsing are all descriptors applied to the disrupted aortic valve. The most common etiology is infective endocarditis (IE). Other causes include myxomatous degeneration, aortic root dissection and traumatic rupture.

Echocardiography provides an invaluable non-invasive means of rapidly evaluating patients with AI in an attempt to determine the etiology and severity of their lesion. Vegetations are suggested by shaggy, fuzzy, nonuniform or dense echoes associated with an aortic valve that has normal motion. Premature mitral valve closure correlates with severe aortic insufficiency and usually indicates imminent need for aortic valve replacement. High frequency diastolic aortic valve flutter and echoes extending from the aortic valve into the left ventricular outflow tract (LVOT) in diastole are M-mode echocardiographic features used to identify a flail aortic leaflet. It has been noted however that these LVOT echoes may be seen with aortic valve

vegetations without actual leaflet disruption.<sup>1</sup> Two dimensional echocardiography (2 D echo) permits visualization of the aortic valve and the LVOT simultaneously. Four patients with anatomic documentation of flail aortic valves are presented with M-mode and 2 D echocardiograms illustrating the utility of both studies in diagnosing a flail aortic leaflet.

### Methods and patients

Four patients admitted to the UCLA Center for the Health Sciences with the clinical syndrome of severe aortic insufficiency were evaluated with M-mode and 2 D echocardiography.

M-mode echocardiograms were performed in the standard manner<sup>2</sup> on a Smith Kline Instrument (SKI) Ekoline 20A Ultrasonoscope with a 2.25 MHz transducer focused at 10 cm. Recordings were made by a Honeywell 1806 A strip chart recorder on Kodak light sensitive paper.

Cross sectional echocardiograms (2 D) were performed with a commercially available mechanical two-dimensional imaging system (SKI Ekosector I) utilizing a 30 degree or wide angle (83 degree) transducer head. The 30 degree angle provided better image quality and structural detail whereas the wide angle was useful for spatial orientation. The standard long axis (LAX) and short axis (SAX) views were obtained in all patients and when technically possible a four chamber apical (hemiaxial) view was also done. Images were recorded on video tape via a Sanyo VTC 1000 cassette recorder for analyses in real time slow motion and single frame format. Individual frames were photographed using a Polaroid system. These pictures are presented in

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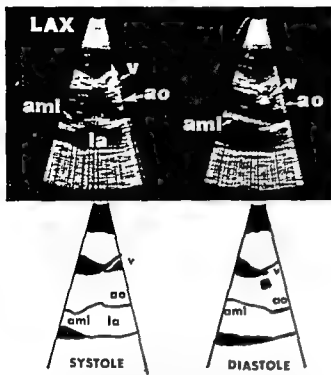


Fig 1 Two dimensional echocardiogram (LAX) in systole and diastole from Case 1 prior to clinical decompensation. The apex is to the left of the figure. A bulky vegetation is noted on the right coronary cusp which moves with the leaflet in systole and diastole. No portion of the leaflet and/or the vegetation extends below the level of the aortic ring. Abbreviations: aml = anterior mitral leaflet; ao = aorta; la = left atrium; LAX = long axis view; v = vegetation.

the text, however, the still photos result in a loss of detail and the inability to appreciate motion. Therefore, the important added information gained from the viewing of real time 2-D echocardiograms cannot adequately be illustrated in this text.

### Case reports

**Case 1** A 31-year-old white male presented with a three-week history of fevers, chills, fatigue, weight loss, arthralgias, and skin lesions. He denied knowledge of a murmur, rheumatic fever, or a history of intravenous drug abuse, but underwent dental work two months previously.

The physical examination revealed aortic insufficiency with no evidence of heart failure. The clinical diagnosis of aortic valve infective endocarditis was made, and the patient was begun on intravenous antibiotics with improvement in symptoms.

The M-mode echocardiogram revealed multiple echoes on the right coronary cusp compatible with valvular thickening and/or vegetations.

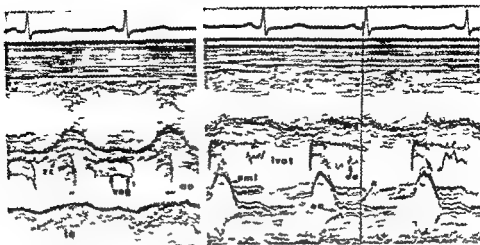
There was diastolic mitral valve fluttering consistent with aortic insufficiency. The left ventricular end-diastolic dimension was 60 mm with increased interventricular septal excursion suggesting left ventricular volume overload. A two-dimensional study confirmed these findings (Fig 1).

Two weeks after admission, blood cultures grew *Kingella ingae*. After four weeks of intravenous penicillin, he was discharged to home on two weeks of oral penicillin. Six weeks after discharge, he again presented with fatigue and rotated orthopnea and palpitations.

M-mode echocardiography revealed that his left ventricular end-diastolic dimension had increased to 70 mm and the left atrium had increased to 40 mm. The echoes consistent with aortic leaflet vegetations persisted in the aortic root, but there were also extra-diastolic echoes in the left ventricular outflow tract consistent with prolapse of an aortic leaflet or part of a vegetation (Fig 2). The mitral valve closed almost completely prior to a very small a-wave, suggesting increased left ventricular diastolic pressure due to severe aortic insufficiency. The two-dimensional study demonstrated an arc-like movement of a portion of the aortic valve into the left ventricular outflow tract during diastole with the anterior aortic wall serving as the hinge point of the motion (Fig 3). This was a distinct change from the previous studies.

Based on the above findings, he was felt to have disrupted at least one aortic leaflet leading to severe aortic insufficiency and acute heart failure. Appropriate cultures were taken and penicillin was restarted. He underwent a porcine heterograft aortic valve replacement 36 hours after admission without having a left-sided cardiac catheterization. At surgery, a trileaflet aortic valve was found, a portion of which appeared to prolapse into the left ventricular outflow tract. All three leaflets were somewhat thickened. The right cusp was covered with multiple friable polypoid appearing vegetations; a second leaflet was perforated, and the third was torn (Fig 4). Organisms were seen in the vegetation, but cultures yielded no growth. He had an uneventful postoperative course and has clinically done well.

**Case 2** A 28-year-old black male first became aware that he had the murmur of aortic insufficiency when he presented at age 26 with paroxysmal



**Fig 2** M-mode echocardiograms from Case 1 after clinical decompensation. The aortic root tracing on the left illustrates the aortic root. The fuzzy echoes of a vegetation(s) on the aortic valve which are best seen in diastole. On the right tracing left ventricular outflow tract extra echoes above the mitral valve imply the prolapse of a portion of the aortic valve and/or a vegetation into the left ventricle. Mitral valve closure effectively occurs at *ec* significantly before the QRS although a small *a* wave is noted. This is consistent with severe aortic insufficiency. Abbreviations: *a* = a wave; *aml* = anterior mitral leaflet; *ao* = aorta; *ec* = early closure; *ee* = extra echoes; *is* = interventricular septum; *la* = left atrium; *lof* = left ventricular outflow tract; *rc* = right aortic cusp; *veg* = vegetation.

mal atrial tachycardia. He had no history of rheumatic fever or drug abuse and the aortic valve lesion was felt most likely to be congenital in origin. One year later his heart was enlarged on chest x ray and digoxin and furosemide were begun.

Over the next year he noted increasing dyspnea on exertion, orthopnea, occasional paroxysmal nocturnal dyspnea, chest and left shoulder pain with heavy exertion, increasing fatigability and occasional palpitations. He was admitted to the UCLA Medical Center for elective cardiac catheterization.

Physical examination revealed a blood pressure of 115/70 mm Hg with bounding arterial pulses. There was no evidence of congestive heart failure. The heart was enlarged. Auscultation revealed a 2/6 mid systolic murmur at the base and a long 2/6 coarse impure decrescendo diastolic murmur which began with the second heart sound and was heard along the left sternal border and at the apex where it developed a rumbling quality. A fourth heart sound was present at the lower sternal border.

M-mode echocardiography demonstrated a dilated left ventricle of 70 mm at end diastole with increased septal excursion consistent with left ventricular volume overload. The left atrium was slightly dilated at 41 mm. There was flutter

ing of the posterior mitral valve leaflet and premature mitral valve closure suggesting severe aortic insufficiency. In addition aortic valve diastolic fluttering suggested a flail aortic cusp (Fig 5). Two dimensional echocardiography revealed diastolic extension of aortic valve tissue into the left ventricular outflow tract (Fig 6). Vegetations were not noted on the M mode or on 2 D echocardiograms. The above findings were diagnostic of a flail aortic valve.

Cardiac catheterization revealed a pulmonary capillary wedge pressure of 15 mm Hg with a left ventricular end diastolic pressure that varied from 30 to 50 mm Hg. The aorta was normal in size and three aortic cusps were visible. There was 4+ aortic insufficiency.

The patient underwent elective aortic valve replacement with a Starr Edward valve. At surgery a trileaflet aortic valve was found with intact commissures and no evidence of vegetations. The noncoronary cusp was redundant and prolapsed into the left ventricular outflow tract. Microscopic examination of the valve revealed diffuse myxomatous changes. The immediate postoperative course was complicated only by pericarditis which responded to indomethacin.

**Case 3** A 30 year old black female heroin abuser was transferred to UCLA for management of progressive heart failure secondary to Group D



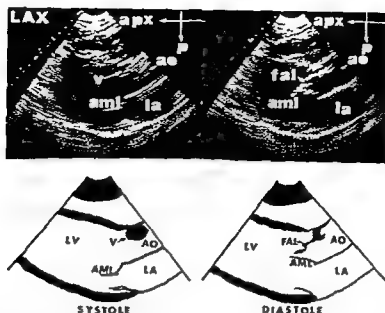


Fig 3 Two-dimensional echocardiogram (LAX) in systole and diastole from Case 1 after clinical decompensation. In systole the aortic leaflets and vegetation are seen only in the aortic root. During diastole the flail portion of an aortic cusp extends into the left ventricular outflow tract almost contacting the anterior mitral leaflet. The dynamic nature of the arc inscribed by the leaflet in moving from aortic root into the left ventricular outflow tract with the anterior aortic wall as its hinge point is impossible to appreciate in these stopframe pictures. Abbreviations: aml = anterior mitral leaflet; ao = aorta; apx = apex; fal = flail aortic leaflet; la = left atrium; LAX = long axis view; p = posterior; v = vegetation.



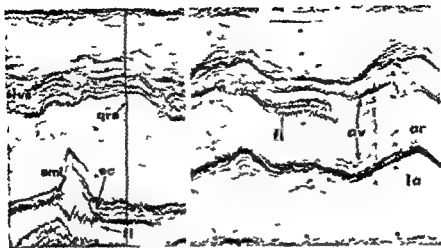
Fig 4 Surgically removed aortic valve from Case 1. The top cusp was extremely thickened and covered with vegetations. The tear in one leaflet and the perforation of the remaining leaflet can easily be appreciated.

streptococcus (*Enterococcus*) endocarditis after two weeks of antibiotic therapy. On admission she was lethargic and tachypneic sitting upright in bed with a blood pressure of 120/40 mm Hg. Jugular vein pulsations were not seen. There were no rales on chest examination. Cardiac examination revealed an enlarged heart with a slight right ventricular impulse felt at the left sternal border. The first heart sound intensity was decreased.

There was a 3/6 midsystolic crescendo decrescendo murmur at the left and right upper sternal borders with radiation to the carotids; a high pitched 3/6 systolic murmur at the apex with radiation into the axilla; and a 3/6 high pitched diastolic murmur which began with the second sound and extended through most of diastole. The liver was 12 cm by percussion and was nonpulsatile. There was minimal peripheral edema and no peripheral stigmata of infective endocarditis (IE).

Chest x-ray demonstrated a markedly enlarged heart with evidence of left and right atrial enlargement and upper lobe pulmonary venous distention. Swan Ganz catheterization revealed pulmonary wedge pressure of 40 mm Hg with large V waves present consistent with significant mitral regurgitation. Mean right atrial pressure exceeded 20 mm Hg. The cardiac output was 2.0 liters per minute. The patient was believed to have severe aortic regurgitation secondary to enterococcal bacterial endocarditis with mitral and tricuspid regurgitation. The etiology of the mitral regurgitation was unclear, possibly representing organic disease secondary to vegetations. The tricuspid regurgitation was thought to be functional.

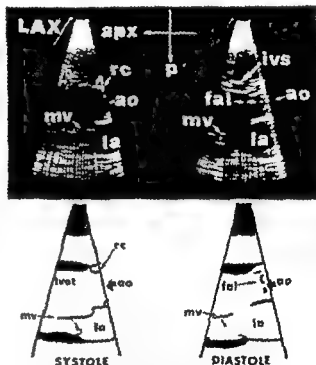
M-mode echocardiography revealed multiple



**Fig 5** M mode echocardiograms from Case 7. On the left tracing fluttering of the posterior leaflet of the mitral valve is noted consistent with aortic insufficiency. The straight black line denotes the beginning of the QRS complex. The closure point (ec) of the mitral valve occurs early (ie) before the QRS and is consistent with severe aortic insufficiency. The right tracing illustrating the aortic root demonstrates high frequency aortic diastolic echoes suggesting a flail aortic cusp. Abbreviations: *ami* = anterior mitral leaflet, *al* = aortic valve leaflets, *ar* = aortic root, *ec* = early closure, *fl* = flutter, *is* = inter-ventricular septum, *la* = left atrium, *qrs* = beginning of QRS complex.

systolic and diastolic echoes in the aortic root consistent with vegetations (Fig 7). There was marked diastolic fluttering of the aortic valve in diastole as well as chaotic systolic fluttering both of which strongly suggested a flail aortic leaflet. Extraneous diastolic echoes present in the left ventricular outflow tract further suggested the diagnosis of a flail aortic leaflet although the presence of a prolapsing vegetation was also possible. Fluttering of the mitral valve in diastole with premature mitral valve closure consistent with severe aortic insufficiency was also present. No definite mitral valve vegetations were noted (Fig 8). The left ventricular end diastolic dimension of 61 mm with increased left ventricular wall excursion suggested left ventricular volume overload. The left atrium was enlarged at 46 mm. Two dimensional echocardiography in real time dramatically demonstrated the prolapse of an aortic cusp and a probable vegetation into the left ventricular outflow tract during diastole (Fig 9). The hinge point of the prolapse was the posterior aortic wall. The mitral valve leaflets appeared to be normal.

On the basis of the above data and the patient's precarious clinical status she was taken to the operating room without prior left heart catheterization. The aortic valve leaflets which were covered with multiple vegetations were resected and were replaced with a porcine heterograft.



**Fig 6** Two-dimensional echocardiogram (LAX) in systole and diastole from Case 2. The aortic leaflets are visualized in the aortic root closely apposed to the aortic wall during systole. In diastole a portion of a leaflet is noted to extend below the level of the aortic valve closure line into the left ventricular outflow tract. This was more easily appreciated on the dynamic motion display. Abbreviations: *ao* = aorta, *apx* = apex, *fal* = flail aortic leaflet, *is* = inter-ventricular septum, *la* = left atrium, *LAX* = long axis view, *lvot* = left ventricular outflow tract, *mv* = mitral valve apparatus, *rc* = right aortic cusp.



Fig 7 M mode echocardiograms of the aortic root from Case 3 In the left tracing of the aortic root and left atrium chaotic systolic flutter of the aortic valve is dramatic and consistent with a flail aortic leaflet The tracing on the right taken from a slightly different angle demonstrates aortic leaflet flutter in diastole as well as systole which also suggests a flail aortic leaflet Extra fuzzy echoes in both systole and diastole are consistent with vegetations Abbreviations ar = aortic root ee = extra echoes fl = flutter la = left atrium lc = possible left coronary cusp nc = noncoronary cusp rc = right coronary cusp

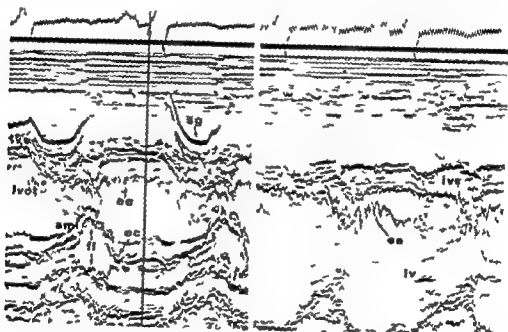


Fig 8 M mode echocardiograms from Case 3 On the left the left ventricle is shown at the level of the mitral valve A Swan Ganz catheter is noted in the right ventricle Diastolic mitral valve flutter and early closure of the mitral valve vegetation severe aortic insufficiency are present Extra coarse fluttering echoes are seen during the diastole in the left ventricular outflow tract These extra echoes are also seen extending during diastole to a level of the left ventricle below the mitral valve in the tracing on the right This combination of findings is consistent with a flail aortic leaflet and a vegetation prolapsing into the left ventricle and resulting in severe aortic insufficiency Abbreviations lv = left ventricle lvot = left ventricular outflow tract av = aortic valve fl = flutter lv = left ventricle lvot = left ventricular outflow tract sg = Swan Ganz catheter

Vegetations on the anterior mitral valve leaflet and interventricular septum were removed A tricuspid annuloplasty was performed

Postoperatively the patient had resolution of her congestive heart failure She was treated with an additional four week course of antibiotics and was discharged five and a half weeks after surgery in stable condition on digoxin only

**Case 4** A previously healthy 16 year old female without known cardiac disease or murmurs was transferred to UCLA for appropriate therapy for presumed infective endocarditis with severe cardiac decompensation She had undergone a therapeutic abortion two weeks prior to admission which was complicated by a purulent sanguinous vaginal discharge

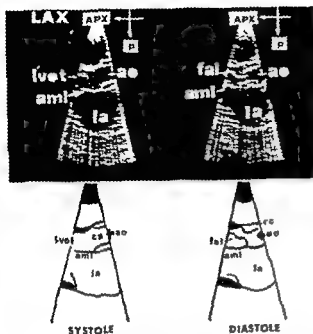


Fig 9 Two dimensional echocardiogram (LAX) from Case 3 The aortic leaflets are visualized in the aortic root in systole During diastole there is abnormal leaflet coaptation and a flail aortic leaflet extends from the posterior aortic wall down into the left ventricular outflow tract A vegetation at the tip of the flail leaflet cannot be ruled out Abbreviations aml = anterior mitral leaflet ao = aorta apx = apex cs = aortic cusps fal = flail aortic leaflet la = left atrium LAX = long axis view lot = left ventricular outflow tract p = posterior rc = right coronary cusp

On initial examination at UCLA she was pale tachypneic and tachycardia with cool mottled skin over the extremities Her blood pressure was 70/30 mm A hyperdynamic left ventricular impulse was palpable in the fifth intercostal space at the midclavicular line A systolic thrill was present at the left lower sternal border The first heart sound was normal with a diminished single second sound A Grade 4/6 systolic murmur was loudest at the left lower sternal border but radiated across the precordium It was characterized as holosystolic versus crescendo decrescendo by various observers A Grade 1 2/6 early decrescendo diastolic murmur was appreciated for the first time There were no gallops The chest examination revealed bibasilar rales There was no peripheral edema Punctate hemorrhages were present on the inner aspect of the left lip A soft supra pubic mass was palpated suggesting an 8 to 10 week size uterus

On M mode echocardiography high frequency diastolic fluttering of the aortic cusp echoes was

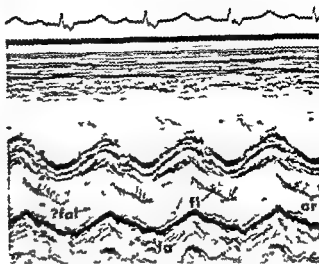


Fig 10 M mode echocardiogram of aortic root from Case 4 High frequency flutter of the aortic valve closure line is noted in diastole suggesting a flail aortic leaflet The posterior noncoronary cusp echo in early systole is shown in the wide-open position but is then noted to drift across the normal systolic aortic opening This may represent the flail leaflet Abbreviations ar = aortic root fal = possible flail aortic leaflet fl = flutter la = left atrium

noted suggesting a flail aortic valve leaflet (Fig 10) The posterior aortic valve cusp was noted to move abnormally across the normal aortic valve opening Mitral valve closure was not premature The left atrium was mildly dilated (40 mm) and the left ventricular diastolic dimension was 50 mm with normal septal and posterior wall motion On the 2 D echocardiogram a portion of the aortic valve extended into the left ventricular outflow tract during diastole and was visualized on both the LAX and SAX views (Figs 11 and 12) Distinct vegetations were not seen on M mode or 2 D echocardiography

The patient was treated for presumed bacterial endocarditis with intravenous antibiotics She underwent emergency dilatation and curettage 12 hours after admission with removal of 25 to 30 grams of necrotic material and port wine colored fluid Her aortic insufficiency murmur became louder The patient suffered two cardiac arrests and was not able to be resuscitated the second time She died 24 hours after admission to UCLA Medical Center

At necropsy the noncoronary cusp of the aortic valve was torn and ragged (Fig 13) There were no gross vegetations present on any of the aortic

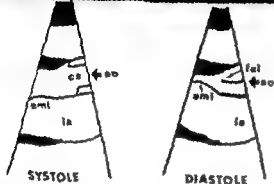
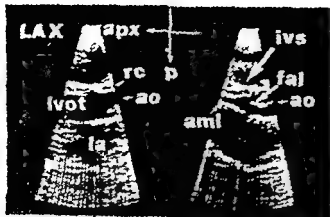


Fig 11 Two-dimensional echocardiogram (LAX) in systole and diastole from Case 4. In systole the aortic valve leaflets are clearly shown to be in the aortic root. The closed mitral valve is clearly visualized. During the early diastolic frame shown the mitral valve is widely open and a portion of an aortic leaflet extends well below the aortic leaflet closure line. Abbreviations: aml = anterior mitral leaflet, ao = aorta, apx = apex, cs = aortic cusps, fal = flail aortic leaflet, ivs = interventricular septum, la = left atrium, LAX = long axis view, lv = left ventricular outflow tract, p = posterior, rc = right cusp.

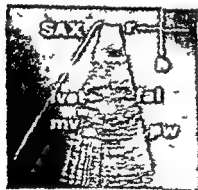


Fig 12 Two-dimensional echocardiogram (SAX) from Case 4. A portion of aortic ventricular outflow tract of these echoes is not co. Abbreviations: fal = flail aortic leaflet, lvot = left ventricular outflow tract, mv = mitral valve, pw = posterior wall, SAX = short axis view.



LAX from Case 4. In systole the left ventricular outflow tract is clearly visualized. In diastole the left ventricular outflow tract is clearly visualized. In diastole the left ventricular outflow tract is clearly visualized. In diastole the left ventricular outflow tract is clearly visualized.

cusps. There was a 1.2 by 0.6 cm perforation of the interventricular septum inferior to this aortic leaflet which extended above the tricuspid valve and communicated with the right atrium. The right atrial side of the perforation was surrounded by friable raised dull red vegetations. The inferior portion of the defect had a smooth border and was felt to represent a preexisting ventricular septal defect. The pulmonary and mitral valves were normal. The left ventricle and left atrium were slightly dilated.

The history, clinical course and pathological findings are consistent with a bacteremia secondary to pelvic manipulation which resulted in the development of endocarditis at the site of a previous small or closed ventricular septal defect. Perforation of the interventricular septum with a left ventricular right atrial shunt developed and the infection eventually involved the (noncoronary) posterior aortic cusp resulting in aortic insufficiency. This process may also have damaged the conduction system leading to asystole and cardiac arrest. All blood cultures and cultures of the necropsy vegetations grew no organisms. Group A alpha hemolytic streptococcus and Group B beta hemolytic streptococci grew from her vaginal cultures and may represent the source of the infection.

## Results

The results are summarized in Tables I and II.

**Case 1** The initial M mode echo was very suggestive of right coronary cusp vegetations, but thickening of the valve was also possible. The dilated left ventricle (LV) with increased wall motion and diastolic mitral valve fluttering were consistent with AI. The 2D echo (Fig 1) was helpful in clearly delineating a very thickened right aortic cusp with normal motion which made the diagnosis of a vegetation much more likely than simply thickening.

When the patient clinically decompensated his M mode echo (Fig 2) showed LVOT echoes in diastole suggesting that a portion of an aortic leaflet or a vegetation was prolapsing into the LVOT. In addition, new early mitral valve closure suggested severe AI. The 2D echo (Fig 3) revealed a flail aortic valve leaflet extending into the LVOT almost touching the anterior mitral valve leaflet. This echo was noted to vibrate



Fig 13 Autopsy specimen from Case 4. The ragged edge (arrow) of the flail noncoronary aortic leaflet is outlined against the perforation of the interventricular septum.

Table 1 Clinico pathological information in four patients with flail aortic leaflets

Case	Sex	Age	Predisposing factors	Organism	Anatomic finding at surgery or necropsy	Left heart cath
1	M	31	Dental manipulation	<i>Kingella kingae</i>	Trileaflet thickened aortic valve with one cusp torn, one perforated and one covered with vegetations	No
2	M	28	None	None	Trileaflet aortic valve with redundant noncoronary cusp and diffuse myxomatous changes	Yes
3	F	3	Heroin abuse	Group D Streptococcus ( <i>Enterococcus</i> )	Probable trileaflet aortic valve with multiple vegetations. Vegetations on anterior mitral valve leaflet and on inter-ventricular septum	No
4	F	18	Ventricular septal defect therapeutic abortion	Not determined	Trileaflet aortic valve with torn posterior cusp. defect of inter-ventricular septum connecting left ventricle and right atrium at site of previous VSD. right atrial opening was surrounded by vegetations	No

Abbreviations: F = female, M = male  
= at necropsy

vigorously. This motion could not be captured on the Polaroid stop frame pictures. The hinge point for the motion of the LVOT echo was at the junction of the leaflet with the aortic root rather than on the body of the leaflet itself, as would be expected with a vegetation alone. These findings

elucidated the cause of sudden cardiac decompensation in a patient with known AI secondary to vegetations and obviated the need for a left heart catheterization in a significantly decompensated patient prior to surgery. At surgery, a torn cusp was noted in addition to a thickened right cusp

Table II M mode echocardiographic findings

Case	LVDD (mm)	LVVO	Early MV closure	Diastolic flutter MV	Diastolic flutter AV	LVOT echoes	Systolic flutter AV	Vegetation
1 pre	67	±a	—	+	—	—	None	S D
post	70	+	+	+	—	+	None	S D
2	70	±a	+	+	+	—	Fine	—
3	61	±b	+	+	+	+	Chaotic	S D
4	50	—	—	—	+	—	None	—

Abbreviations and symbols: AV = aortic valve; D = present in diastole; LVDD = left ventricular diastolic dimension; LVOT = left ventricular outflow tract; LVVO = left ventricular volume overload; MV = mitral valve; post = after clinical decompensation; pre = before clinical decompensation; S = present in systole; + = present; — = absent; ± = increased left ventricular dimension with (a) increased septal motion and normal LV posterior wall motion or (b) increased posterior wall motion and normal septal wall motion.

densely covered with nonmobile vegetations.

**Case 2** The M mode echocardiogram revealed a dilated left ventricle with increased septal motion consistent with left ventricular volume overload (LVVO) and a dilated left atrium. Severe AI was suggested by the combination of a fluttering mitral valve in diastole and early mitral valve closure (Fig 5). Rapid high frequency oscillations of the aortic valve in diastole were prominent and suggested a flail leaflet (Fig 5). On 2 D echo (Fig 6) a portion of the aortic valve was observed to prolapse into the LVOT, confirming the diagnosis suggested on M mode echocardiography. Still frame Polaroid pictures could not capture this motion well. There was no suggestion of vegetations on either study. At surgery a redundant noncoronary cusp which prolapsed into the LVOT was noted. There were no vegetations.

**Case 3** The M mode echocardiogram (Fig 7) revealed striking fluttering of the aortic valve leaflets in both diastole and systole, chaotic and coarse in some views, suggesting a flail leaflet (either the left or noncoronary cusp). The views of the left ventricle both at and below the mitral valve demonstrated coarse diastolic extra echoes in the LVOT (Fig 8). Either a flail leaflet and/or a vegetation on the ventricular surface of the aortic valve could produce the above picture. Two-dimensional echocardiography (Fig 9) dramatically demonstrated that in early diastole the posterior cusp seen on the long axis view abruptly moved (within one frame) into the LVOT with a whip-like motion. The pivot point of this whip-like motion was clearly the aortic wall rather than the aortic leaflet itself. In addition the two leaflets seen on the LAX view did not coapt in diastole. These findings were

diagnostic of a flail leaflet. Therefore the etiology of this patient's clinical compromise was determined and surgery was performed without a left heart catheterization. A vegetation at the tip of the flailing leaflet could not definitely be ruled out. Multiple vegetations were noted at surgery but a comment as to their mobility or exact location was not made.

**Case 4** Striking M mode findings (Fig 10) in this case were rapid high frequency diastolic vibrations of the aortic valve and abnormal anterior systolic motion of the posterior aortic cusp. These two findings were highly suggestive of a flail aortic leaflet. There was no evidence of vegetations.

On 2 D echo a portion of the aortic valve extended into the LVOT where it vibrated vigorously. It was demonstrated on both the LAX and SAX views and was felt to represent a flail aortic leaflet (Figs 11 and 12). This was the only case in which LVOΓ echoes were noted on the SAX view. The etiology of the flail leaflet was not suggested by either the M mode or 2 D study. This patient had no vegetations on her flail aortic leaflet at autopsy, although vegetations were present on the right atrial side of the interventricular defect.

## Discussion

The echocardiographic manifestations of a ruptured aortic valve leaflet were initially described by Lee and colleagues. In four patients with subsequent anatomical confirmation they noted a band of high frequency echoes (HFE) during early to mid diastole in the aortic root echograms. There was no comment on the etiology of the ruptured leaflets.

Wray first described the M mode findings of a

flail aortic valve leaflet in bacterial endocarditis. Dense disorganized diastolic echoes were noted in the aortic root and in the LVOT in the first patient he described. In a series of five patients with aortic valve endocarditis and aortic insufficiency he noted "coarse or thin diastolic echoes in the aortic root which move erratically or vibrate" and felt these suggested that at least a portion of the aortic valve was flail.

The presence of diastolic LVOT echoes secondary to primary aortic valve disease was noted by Gottlieb and associates<sup>1</sup> in two patients with *Candida* endocarditis. However these echoes were felt to represent the bulky fungal vegetations on the aortic valve rather than a flail leaflet.

A flail aortic valve leaflet due to myxomatous degeneration in three patients and due to bacterial endocarditis in two was documented pathologically by Whipple and co-workers. They noted both (1) diastolic LVOT echoes and (2) diastolic fluttering of the aortic valve but added (3) coarse systolic oscillations of the aortic cusp echoes to the described M mode manifestations of flail aortic valve leaflets. They interpreted the presence of (2) to be secondary to AI alone but the combination of 1 and 2 to be diagnostic of a flail or prolapsed leaflet. A fourth case of a flail aortic valve secondary to myxomatous degeneration with the three echocardiographic features described above was reported by Estevez and associates.

Roy and colleagues<sup>2</sup> noted that eight of 32 patients with bacterial endocarditis had LVOT echoes that merged into diastolic aortic valve vibrations. In this series LVOT echoes could be seen with vegetations alone or with actual valvular disruption.

Chandraratna and co-workers<sup>3</sup> described abnormal LVOT echoes in four patients with severe AI. Three had bacterial endocarditis and one had myxomatous degeneration of the aortic valve (floppy aortic valve). High frequency diastolic fluttering of the aortic valve was noted in the patient with myxomatous degeneration and was similarly seen in another patient with a floppy aortic valve also reported by the same authors.

In six other case reports of flail or ruptured aortic valves in patients with definite or presumptive IE the echo findings consisted of various

combinations of the diagnostic criteria summarized above.

Kleiner and associates<sup>4</sup> described two patients with IE and surgically confirmed flail aortic leaflets in whom dense aortic root echoes were noted in systole but not in diastole with associated diastolic LVOT echoes. The dense systolic echoes presumably represented the fluttering flail aortic leaflet which during diastole was present only in the LVOT and was represented by the echoes seen there. These workers concluded that this constellation of findings was pathognomonic of a ruptured aortic cusp.

Yoshikawa and colleagues<sup>5</sup> reported a case in which the M mode echo revealed diastolic fuzzy aortic valve echoes with fine fluttering diastolic fluttering LVOT echoes and coarse systolic fluttering of the aortic valve. These findings were consistent with a flail aortic valve and/or a vegetation on the aortic valve which was large and/or mobile. Ultrasonic cross section views in the long axis demonstrated a 3 cm long vegetation extending from the midpoint of aortic valve coaptation into the LVOT in diastole and continuous with the noncoronary cusp in the aortic root during systole. The observation that the hinge point of the lesion appeared to be the edge of the posterior cusp rather than the aortic wall led them to conclude the abnormal echo represented a large mobile vegetation. At surgery a 3 cm long cordlike vegetation was attached to the ventricular surface of the noncoronary cusp.

Two additional examples of surgically confirmed aortic valve IE have been reported with 2 D echocardiography demonstrating vegetations that protruded into the LVOT.<sup>6</sup> In one case a long thin vegetation was visualized moving from aortic root to LVOT in systole and diastole respectively. Coaptation of the aortic cusps was seen in diastole and the vegetation extended down from the midpoint of coaptation into the LVOT. In the second case bulky vegetations were seen on all three cusps on 2 D echo which extended below the plane of aortic valve closure into the LVOT. Thus in one case LVOT echoes were due to a mobile vegetation and in the second they were secondary to large bulky vegetations. In both cases the hinge point of the abnormal echoes was the aortic cusp rather than the aortic wall and diastolic coaptation of the cusps was visualized. This made a flail leaflet less likely.



M mode findings in these cases were not detailed

A fourth case in which 2 D echo was helpful in clarifying the M mode findings and in diagnosing both a vegetation extending into the LVOT and an aortic root abscess was recently reported

In three of our four patients with a flail aortic leaflet the diagnosis of severe acute AI was suggested by the combination of diastolic MV flutter and early MV closure seen on the M mode echocardiogram. Echocardiographic evidence of aortic valve vegetations was present in the two patients with surgically documented aortic valve vegetations. Diastolic flutter of the aortic valve was present in Cases 2, 3, and 4. LVOT echoes were present in Cases 1 and 3, and coarse systolic flutter of the aortic valve was present in Case 3. The high frequency diastolic flutter of the aortic valve is the most specific M mode finding of a flail aortic leaflet and was present in three of the four cases. The additional coarse chaotic systolic flutter of the aortic valve seen in Case 3 further supported this diagnosis. Case 1 however had neither of these findings but had LVOT echoes which could have been due to a flail leaflet and/or a vegetation. The 2 D echocardiogram in Case 1 was necessary to distinguish between these two possibilities.

On two dimensional echocardiography, in each case a portion of the aortic leaflet extended into the LVOT demonstrating a flail leaflet. This was best seen on the LAX view but was also captured on the SAX view in Case 4. The distinction between a flail leaflet and a vegetation was made by noting the location of the hinge point of the motion of the abnormal echoes into the LVOT. The hinge point in these four cases was the aortic wall in contrast to the edge of the aortic leaflet as had been reported with vegetations. In Case 3 it is possible that a vegetation was present at the tip of the leaflet in addition to its being flail. Abnormal coaptation of aortic leaflets when detected as in Case 3 is further 2 D evidence for a flail leaflet. Unfortunately, the above findings are best appreciated in real time and are difficult to convincingly capture in still frame photographs.

In summary, in three patients a flail aortic leaflet could be diagnosed with M mode echocardiography alone although the 2 D echo provided important confirmation. In Case 1 the 2 D echo allowed the distinction of a flail leaflet versus a prolapsing vegetation to be made. It should be

acknowledged, however that in patients with IE and severe AI the distinction between a flail leaflet and a vegetation often can be a moot point and may not affect the eventual treatment plan.

### Summary

Four patients with documented flail aortic valve leaflets were studied using M mode and two dimensional echocardiography (2 D echo). Two had aortic valve endocarditis, one had endocarditis involving a congenital heart defect and one had a myxomatous aortic valve. Mitral valve flutter and early mitral valve closure led to the diagnosis of severe aortic insufficiency in three patients. Diastolic aortic valve flutter considered to be specific for a flail aortic leaflet was present in three patients. In the fourth patient left ventricular outflow tract (LVOT) echoes were present but did not distinguish between a flail aortic leaflet and an aortic vegetation. Two D echo confirmed LVOT echoes in all patients. Discrimination between a flail leaflet and a vegetation without leaflet disruption was accomplished by noting the hinge point of the LVOT diastolic echoes which was the aortic wall in patients with a flail leaflet.

The combination of these M mode and 2 D echocardiographic findings permitted the diagnosis of a flail aortic leaflet to be made accurately and noninvasively. In two patients surgery was performed without prior cardiac catheterization.

We express our gratitude to Diane Kennedy and Stephanie Thessomboom for their expert technical assistance.

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# Relationship of plasma anti-heparin activity and platelet survival time in coronary disease\*

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Platelets probably contribute to the development of atherosclerosis and its complications. Platelet survival time is shortened in patients with atherosclerotic coronary disease.<sup>1,2</sup> The storage organelles of platelets contain proteins with heparin neutralizing activity which are released into plasma both in vivo and in vitro in response to platelet aggregating agents.<sup>3,4</sup> Increased heparin neutralizing activity has been observed in patients with coronary disease.<sup>5-8</sup> A number of drugs with effects on laboratory tests of platelet reactivity have been identified and one of these drugs, sulfinpyrazone, has been shown to decrease sudden cardiac deaths in survivors of myocardial infarction.<sup>10</sup>

In the present study, platelet survival time and plasma heparin neutralizing activity were measured in men with coronary disease and the effects of several platelet suppressant drugs on these two tests of platelet reactivity were defined.

## Patients

Studies were undertaken in 75 men with coronary artery disease. All men had undergone coronary arteriography for evaluation of coronary

disease. Thirty three men had clinical and electrocardiographic evidence for past transmural infarction and 62 men were having angina at the time of study. All men had been in a stable clinical condition for at least three months prior to study.

## Methods

Platelet survival time was measured by labeling the platelets from 300 to 400 ml of the patient's blood with <sup>51</sup>Chromium (100 to 150 microcuries).<sup>11</sup> A single exponent was fitted to seven days of platelet count rate data to obtain the half time. This was performed with a computer using least square analysis. In 26 normal men platelet survival half time averaged  $37 \pm 0.03$  ( $\pm$  SEM) days. The range of platelet survival half time was 33 to 42 days.

Plasma heparin neutralizing activity was measured as the patient's heparin thrombin clotting time (platelet poor plasma) divided by the clotting time of normal substrate. The result was expressed as a ratio with an average value for 20 normal men of  $1.10 \pm 0.01$  and a normal range of  $0.96 \pm 1.24$  ( $\pm$  2 SD). Abnormally increased levels of plasma heparin neutralizing activity would be expressed as a ratio less than 0.96.

Heparin neutralizing activity and platelet survival time were performed simultaneously over a week's time. Following control measurements sulfinpyrazone (800 mg orally per day), indomethacin (100 mg orally per day) or aspirin (1200 mg orally per day) alone and in combination with dipyridamole (100 mg orally per day) were administered and studies were repeated in two to three months. In this study patients were not randomly assigned to the treatment groups.

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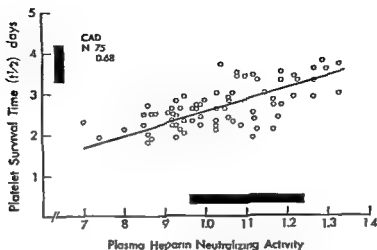


Fig 1 Relation ship between platelet survival time and plasma heparin neutralizing activity in men with coronary artery disease (CAD). The solid bars represent the normal ranges

A second study was undertaken in 12 of these men to define the time course of alteration of heparin neutralizing activity. Plasma heparin neutralizing activity was determined each day for eight days after initiating treatment with sulfinpyrazone and after placebo (crossover blinded design).

Statistical analysis was performed using Student's *t* test. All patients understood the purpose and the risk of the study and agreed to participate.

## Results

Platelet survival time was shortened ( $< 3.3$  days) in 60 men (80%) and averaged  $2.6 \pm 0.06$  days ( $t_{1/2} \pm \text{SEM}$ ,  $P < 0.001$  vs normal). Heparin neutralizing activity was increased (ratio decreased) in 26 men (35%) (ratio patient to substrate  $< 0.96$ ) and averaged  $1.04 \pm 0.02$  (average ratio  $\pm \text{SEM}$ ,  $P < 0.001$  vs normal). These two measurements of platelet reactivity appeared to have a relationship with each other (correlation coefficient  $r = 0.68$ ) (Fig 1). Of the 15 men with normal platelet survival time all had normal heparin neutralizing activity. Of the 60 men with shortened platelet survival 26 had abnormal heparin neutralizing activity and this test was normal in the other 34 men. Thus in men with coronary disease these two tests of platelet reactivity appear to relate to each other but platelet survival time is more sensitive for the presence of coronary artery disease than is plasma heparin neutralizing activity. Of the 33 men

with a history of transmural infarction 26 (79%) had shortened platelet survival and 13 (39%) had increased heparin neutralizing activity. These frequencies are not different from the frequencies for the group of men without a history of infarction or for the whole group of men with coronary disease.

Twenty men with shortened platelet survival received sulfinpyrazone and platelet survival was increased by at least 0.02 days in 14 (70%) ( $2.5 \pm 0.07$  to  $2.8 \pm 0.09$  days,  $P < 0.01$ ). Heparin neutralizing activity was decreased by sulfinpyrazone (ratio increased) ( $1.02 \pm 0.03$  to  $1.19 \pm 0.01$ ,  $P < 0.001$ ) and 18 (90%) had an increase in this ratio by at least 0.03. All three of these men with abnormal control values for heparin neutralizing activity had an alteration with sulfinpyrazone.

Indomethacin also increased platelet survival time ( $2.4 \pm 0.08$  to  $2.7 \pm 0.08$  days,  $N = 16$ ,  $P < 0.01$ ) and 11 (69%) had an increase. Heparin neutralizing activity was altered by indomethacin ( $0.98 \pm 0.02$  to  $1.15 \pm 0.02$ ,  $P < 0.001$ ) and 14 (88%) had a decrease in activity. All of these 16 men had shortened control platelet survival and three had abnormal control values for heparin neutralizing activity.

Twenty-four men received aspirin 1200 mg orally per day for two months and then dipyridamole 100 mg orally per day with aspirin for an additional two months with studies repeated. Aspirin had a small, but significant effect on platelet survival time ( $2.4 \pm 0.06$  to  $2.6 \pm 0.07$  days,  $P < 0.05$ ) and 10 men (42%) had an increase

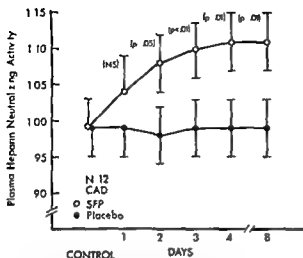


Fig 2 Alteration of plasma heparin neutralizing activity by sulfipyrazone (SFP) in men with coronary artery disease (CAD). The bars represent the standard error.

in platelet survival. Aspirin had a more marked effect on heparin neutralizing activity ( $0.99 \pm 0.03$  to  $1.07 \pm 0.02$ ,  $P < 0.01$ ) with 17 men (71%) having an alteration. With dipyridamole and aspirin a further increase in platelet survival time ( $30 \pm 0.09$  days,  $P < 0.001$ ) and a further decrease in heparin neutralizing activity ( $1.16 \pm 0.02$ ,  $P < 0.001$ ) was observed. All of these men had shortened control platelet survival and five had increased control values for heparin neutralizing activity.

In the platelet suppressant drug studies all men who had an increase in platelet survival also had a decrease of plasma heparin neutralizing activity. Measurement of heparin neutralizing activity was more sensitive in respect to demonstration of a drug effect. In addition the alteration of both tests by aspirin was less marked than the alteration by the other drugs.

Using a blinded cross over design sulfipyrazone and placebo were administered to 12 men with coronary disease and shortened platelet survival time and daily measurement of plasma heparin neutralizing activity was undertaken. There was a stepwise increase in the ratio (decrease in activity) occurring by the second day with maximal values reached by the fourth day in all men (Fig 2). With placebo heparin neutralizing activity was not altered by 0.03 in any patient. Thus sulfipyrazone appears to act promptly to decrease heparin neutralizing activity in men with coronary artery disease.

## Discussion

The present study confirms previous studies suggesting that platelet survival time is shortened in most patients with atherosclerotic coronary disease.<sup>1</sup> Platelet survival time and plasma heparin neutralizing activity appear to be related to each other although this heparin neutralizing activity was within the normal range for most patients with coronary artery disease. O'Brien and associates<sup>8</sup> observed substantially increased heparin neutralizing activity in patients within several days of an acute myocardial infarction. Heparin neutralizing activity decreased towards normal in these patients during convalescence (three months). Duna and associates<sup>9</sup> found increased heparin neutralizing activity in several groups of patients with coronary disease, including patients in a stable clinical situation during acute myocardial infarction or during unstable angina. Our patients were all in a stable clinical state and there were no differences in heparin neutralizing activity between men with and without a history of infarction.

The relationship between plasma heparin neutralizing activity and platelet survival time suggests that this neutralizing activity reflects platelet reactivity. Platelets contain and release a low molecular weight protein (or proteins) platelet factor four which has heparin neutralizing activity. It is probably too simplistic to suggest that plasma heparin neutralizing activity measures platelet heparin neutralizing activity since both erythrocytes and leukocytes have heparin neutralizing activity<sup>12,14</sup> without having the platelet factor four protein.<sup>11</sup>

Measurement of plasma heparin neutralizing activity does appear to be a sensitive indicator of platelet suppressant drug effect. With this test sulfipyrazone, indomethacin and dipyridamole in combination with aspirin were observed to have a greater effect on plasma heparin neutralizing activity than on platelet survival time. Aspirin was shown to have an effect on both platelet survival time and heparin neutralizing activity but this effect was less marked than with the other drugs. These data suggest that indomethacin is a platelet suppressant agent which is not surprising in that it shares pharmacologic actions with sulfipyrazone. In addition sulfipyrazone appears to act quickly as supported by the decrease in plasma heparin neutralizing activity.

ity observed as soon as 48 hours after initiating treatment

Although platelet suppressant therapy has been suggested for the prevention of thrombosis it is unclear which drugs and which clinical situations might benefit from their use<sup>1</sup> Platelet suppressant drugs have been shown to decrease thromboembolism in patients with prosthetic cardiac valves, external elastic arteriovenous shunts,<sup>2</sup> recurrent venous thrombosis<sup>3</sup> and may be effective in preventing venous thrombosis after major surgery<sup>4</sup> and in preventing stroke and death in patients with atherosclerotic cardiovascular and cerebrovascular disease<sup>1</sup> The effectiveness of these drugs in decreasing thrombosis and in altering plasma heparin neutralizing activity would suggest that these tests are of value in thrombotic diseases and that plasma heparin neutralizing activity may be measuring platelet anti heparin activity. Radioimmunoassay has been developed which appears to measure platelet factor four<sup>5</sup> and it will be necessary to correlate this measurement with heparin neutralizing activity and with platelet survival in patients with thrombosis

## Summary

Platelet endothelial interaction probably plays a role in the development of atherosclerotic vascular disease and its complications Platelet survival time has been found to be shortened and plasma anti heparin activity has been shown to be increased in patients with coronary atherosclerosis Platelet survival (autologous labelling with

Chromium) and plasma anti heparin activity (heparin thrombin clotting time of platelet poor plasma) were measured in 75 men with coronary artery disease Platelet survival was shortened ( $< 33$  days) in 60 men (80%) and averaged  $26 \pm 0.06$  days (AVE  $\pm 1/2 \pm$  SEM normal  $117 \pm 37 \pm 0.03$  days  $N = 28$   $P < 0.001$ ) Anti heparin activity was abnormal ( $< 0.96$ ) in 26 men (33%) and averaged  $1.04 \pm 0.02$  (ratio patient to blank seconds/seconds, normal ratio  $1.10 \pm 0.01$   $N = 25$   $P < 0.01$ ) Platelet survival time correlated with anti heparin activity ( $r = 0.68$ ) Sulfapyrazone (800 mg daily) and indomethacin (100 mg per day) increased platelet survival and decreased heparin neutralizing activity Dipyrindamole (100 mg orally per day) in combination with aspirin (1200 mg per day) increased platelet

survival and decreased anti heparin activity but aspirin alone had a comparatively weak effect on these tests Results suggest that plasma heparin neutralizing activity correlates with platelet survival time in men with coronary artery disease Sulfapyrazone, indomethacin and dipyrindamole in combination with aspirin alter platelet survival and heparin neutralizing activity but aspirin alone has a comparatively weaker effect

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## The effect of acebutolol on cardiac arrhythmias in patients with chronic coronary artery disease

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The use of beta adrenergic blocking agents in the treatment of cardiac arrhythmias is gaining increasing importance particularly in patients with concomitant coronary artery disease or hypertension. In view of the well known extracardiac side effects efforts are directed toward development of agents with specific action on cardiac beta receptors. Acebutolol has been shown to be a relatively cardioselective drug with weak intrinsic sympathomimetic activity. While its short-term effect in decreasing the incidence of ventricular extrasystoles is well documented it is not known whether acebutolol is also capable of lessening the severity of ventricular arrhythmias and the frequency of exercise induced arrhythmias. This double blind cross-over clinical trial was therefore designed to quantitate the effects of acebutolol on the grade of ventricular arrhythmias and on the incidence of stress induced arrhythmias.

### Materials and methods

**Subjects** We studied 15 patients (12 men and three women with a mean age of  $57 \pm 10.6$  years) who had chronic coronary artery disease documented by old myocardial infarction or abnormal coronary arteriograms ( $\geq 75\%$  luminal narrowing of at least one of the main vessels) or patients who had undergone an aortocoronary bypass operation. Patients with conduction disturbances

congestive heart failure chronic obstructive lung disease hypotension or severe metabolic disease were excluded from the study. Except for digitals and nitroglycerin no cardioactive drugs were permitted. Patients entered the study on the basis of a preliminary 4 hour Holter ECG in which at least one episode with a minimum of 12 VPBs/minute or arrhythmias of a higher degree were required.

**Drug testing** The investigation was carried out in two periods of four weeks each. In the first period patients were randomly started on an oral dose of either placebo or acebutolol 200 mg twice daily. At the end of weeks 2, 4, 6 and 8 a 4 hour long term ECG (LECG) was recorded. At the end of weeks 4 and 8 patients were in addition exercised on a bicycle ergometer with 80 watts. The ECG was written continually throughout the exercise test (6 minutes) as well as after exercise (5 minutes) to permit evaluation of arrhythmias. For the interpretation of exercise tests we noted the highest heart rate reached and the number of ventricular premature beats (VPBs). LECGs were classified according to the highest grade of arrhythmias reached using a modified classification of Lown:

0 = no VPBs

1 = < 12 VPBs/minute

2 =  $\geq 12$  VPBs/minute

3 = multifocal VPBs

4 = 2 to 4 VPBs in a row and/or R on T phenomenon

5 = ventricular tachycardia ( $\geq 5$  VPBs in a row)

The worst of the two placebo and acebutolol tracings were compared.

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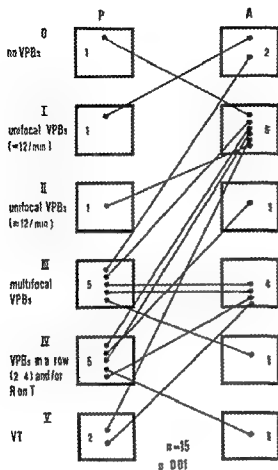


Fig 1 Severity of ventricular arrhythmias during Holter monitoring. P = placebo. A = acebutolol. Note that quantification of VPBs is based on a one minute write out of the worst episode recorded.

For statistical analysis we used the Wilcoxon test for paired samples. Data are reported as mean  $\pm$  standard error of the mean ( $\bar{x} \pm \text{SEM}$ ).

### Results

The results of the Holter recordings are shown in Fig 1. Comparison of the grade of arrhythmias in the placebo and acebutolol periods disclosed a favorable effect of acebutolol in 10 patients, a worsening in three, and no effect in two patients. Classification of the most severe arrhythmia recorded nevertheless revealed a decrease from an average grade of  $3.2 \pm 0.3$  (placebo) to  $1.9 \pm 0.38$  (acebutolol) ( $p = 0.01$ ). While on placebo 20% of our patients were in Class 0 to II and 80% were in Class III to V, whereas during the acebutolol period the corresponding proportions were 60% and 40%.

During and after exercise, acebutolol decreased the incidence of ventricular arrhythmias from  $1815 \pm 77$  VPBs in the placebo period to

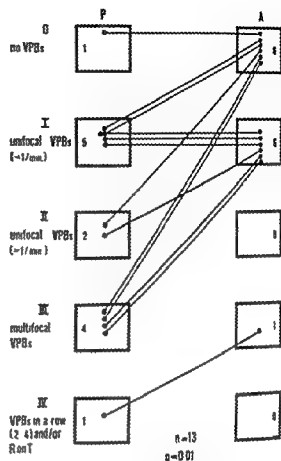


Fig 2 Severity of exercise induced ventricular arrhythmias during administration of placebo (P) and acebutolol (A).

$346 \pm 17$  VPBs in the acebutolol period ( $-81\%$ ,  $p < 0.0025$ ). The maximum heart rate reached during exercise was slower in the acebutolol group ( $96.2 \pm 4.7$ ) than in the placebo group ( $121.8 \pm 7.1$ ) ( $p < 0.0005$ ). Grading of arrhythmias induced by exercise revealed a significant improvement from a mean of  $1.92 \pm 0.33$  (placebo) to  $0.69 \pm 0.24$  (acebutolol) ( $p < 0.01$ , Fig 2).

### Discussion

There is general agreement in the literature that in patients with coronary artery disease ventricular arrhythmias may presage sudden death. Although it is not quite as clear to what extent treatment of these arrhythmias influences mortality from sudden death, it is a commonly used policy to treat certain ventricular arrhythmias in the hope to improve prognosis. Despite intense efforts, an ideal antiarrhythmic drug which reliably suppresses ventricular arrhythmias and which has no serious side effects has not yet been found. Beta blocking agent

would appear to be particularly well suited for patients with coronary artery disease since they are part of the standard medical regimen in the treatment of angina pectoris. Their antiarrhythmic action may be a direct consequence of adrenergic blockade and/or a membrane stabilizing property or it may be mediated by its favorable effect on myocardial ischemia. Clinical efficacy of single and multiple doses of acebutolol in lowering the incidence of ventricular arrhythmias has been shown previously.<sup>1</sup> The present study disclosed ventricular arrhythmias of a significant but lower grade after oral administration of acebutolol. However, despite this significant difference, a slight worsening was seen in three patients. From our study, in which acebutolol was given in a dosage of 200 mg twice daily, it would appear that lower doses of this drug than reported by Gradman and colleagues (300 mg three times daily) achieve satisfactory results.

One can conclude that acebutolol is a well tolerated drug which favorably influences incidence and severity of ventricular arrhythmias even in moderate oral doses in patients with chronic coronary artery disease.

### Summary

The effect of the beta blocking drug acebutolol on the severity of cardiac arrhythmias and the incidence of exercise induced arrhythmias was studied in 15 patients with chronic coronary artery disease using ambulatory Holter monitor-

ing and bicycle ergometry. We found a significantly lower grading of arrhythmias both on long term ECGs and during and after exercise. Furthermore, there was a significant decrease in the incidence of VPBs during and after exercise ( $18.15 \pm 7.7$  on placebo vs  $3.46 \pm 1.7$  on acebutolol). It is concluded that acebutolol favorably influences the incidence and severity of ventricular arrhythmias in patients with chronic coronary artery disease.

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# Clinical and morphological features of human hypertensive-diabetic cardiomyopathy

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Chronic congestive heart failure is a common and serious complication of diabetes mellitus in man<sup>1</sup>. Although usually ascribed to the effects of obstructive extramural coronary artery disease, recent data suggest that myocardial dysfunction may be associated with diabetes mellitus in the absence of extensive coronary artery atherosclerosis<sup>2-4</sup>. These observations have given rise to the concept of diabetic cardiomyopathy. The pathogenesis of this cardiomyopathy is unknown but proposed mechanisms include small vessel (intramural) coronary artery disease<sup>5-7</sup>, interstitial myocardial accumulation of glycoprotein and collagen<sup>8</sup>, and metabolic alterations of the diabetic myocardium<sup>9-11</sup>. To date most morphological studies of the diabetic heart in failure have not revealed sufficient abnormalities of the myofiber or interstitium to reasonably account for marked diminution of ventricular function.

Although there is an increased prevalence of hypertension among diabetic patients, the role of high blood pressure in the genesis of clinical diabetic myocardial dysfunction has not been clear. Most published studies of diabetic cardiomyopathy have specifically excluded patients with diastolic hypertension from analysis. However, hypertension may play an important role in

the development of cardiomyopathy in diabetes for it is felt to have adverse cumulative effects on the cardiovascular system in these patients<sup>12</sup>.

The purpose of this report is to describe detailed clinical and pathological observations in a consecutive series of nine diabetic patients with severe congestive heart failure who had minimal extramural coronary artery disease. Of significance, although elevated blood pressure was not a criterion for inclusion in this study, all diabetic patients with cardiomyopathy examined in our institution during a two year period were found to have clinically documented hypertension. These patients were compared to appropriate control groups in an attempt to delineate the specific effects of diabetes mellitus and concurrent hypertension on the heart. We believe that the evidence presented below supports the hypothesis that in at least some patients, diabetic cardiomyopathy results from the combination of diabetes mellitus and high blood pressure acting in tandem.

## Materials and methods

The autopsy records of the Bronx Municipal Hospital Center and the Hospital of the Albert Einstein College of Medicine were reviewed for the years 1976 and 1977. All adult patients with diabetes mellitus for more than 5 years duration and with a history of chronic congestive heart failure were selected for further study. Only patients with diabetes mellitus requiring oral hypoglycemic agents or insulin therapy were included. Patients under 40 years of age or patients with severe extramural coronary artery

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disease (greater than 50% narrowing of the lumen) were excluded. Also eliminated were patients with a history of alcohol abuse, hemochromatosis, rheumatic or degenerative valvular disease, syphilis, or systemic vasculitis. Nine patients were identified who fulfilled these criteria.

The clinical histories and general postmortem findings were carefully reviewed. Patients were classified as hypertensive if the systolic pressure was greater than 140 mm Hg and/or the diastolic pressure was greater than 90 mm Hg on more than one determination or if there was a history of documented high blood pressure requiring medical treatment prior to terminal hospitalization. Clinically apparent symptoms of ischemic heart disease such as angina pectoris or previous myocardial infarction were noted as were complications of diabetes mellitus such as peripheral vascular disease, nephropathy, neuropathy, or retinopathy. The diagnosis of congestive heart failure was based on physical examination and/or historical evidence of recurrent pulmonary edema, dyspnea, orthopnea, and peripheral edema requiring appropriate therapy.

The postmortem examinations were supervised by one of us (S M F) in all but one instance. The hearts were sectioned either with horizontal slices from apex to base or were opened in standard fashion with cuts parallel to the long axis of the septum. Heart weights and ventricular wall thickness at the outflow tract were recorded. Multiple random blocks of myocardium (a minimum of six) were removed from all cavities as well as portions of obviously necrotic or fibrotic tissue. The coronary arteries were sectioned at 5 mm intervals with histology performed on all rings demonstrating luminal compromise. All tissues were fixed in 3.7% formaldehyde and were processed routinely. Tissues were stained with hematoxylin-eosin, Masson's trichrome stain for connective tissue, periodic acid-Schiff with and without diastase pretreatment, and van Gieson's elastic stain.

The microscopic analysis was semi-quantitative and was based on studies of all histologic sections from each case. The sections were measured to determine the amount of tissue per slide in square centimeters. The slides were scanned at 10 $\times$  magnification and the number of vessels approximately 50 to 200 microns in diameter as determined by an eyepiece micrometer were evaluated. Vessels with sclerosis and/or perivascular

fibrosis were tabulated and a numerical ratio of abnormal vessels per square centimeter of tissue was calculated for each slide and for the entire case. Vascular sclerosis was defined as vessels with intimal and medial hyperplasia and/or fibrosis, elastic tissue proliferation, and the deposition of PAS positive material in the vessel wall. Perivascular fibrosis was defined as the presence of perivascular connective tissue which encroached upon and appeared to involve the adjacent myocardium. Both of these parameters of intramycocardial small vessel disease have been described previously.<sup>10</sup>

Two types of pathological fibrotic myocardial lesions were described and graded. Interstitial fibrosis was defined as areas of collagen deposition surrounding small vessels (less than 50 microns in diameter) and encircling individual or groups of myocardial fibers. These were graded 1+ if patchy, 2+ if they involved less than one third of the sections, 3+ if they involved one third to two thirds of the sections, and 4+ if they occurred in more than two thirds of the sections. Scars were defined as confluent areas of fibrosis more than 500 microns in greatest dimension. These were graded as 1+ if seen rarely, 2+ if seen with moderate frequency, and 3+ if seen frequently in each of the tissue sections examined.

Myocytolysis was defined as a process involving groups of necrotic myocardial cells demonstrating loss of cytoplasmic constituents, often with preservation of nuclear detail eliciting a mononuclear cellular inflammatory response and usually associated with interstitial hemorrhage. Contraction band type of necrosis was also included in this category. The lesions were graded as 1+ 2+ or 3+ based on their frequency in each slide and in the entire case, similar to the quantitation of focal scars as described above. PAS positive material evaluated in diastase treated sections was graded in a like manner.

Upon recognition that our original study group consisted of nine patients with hypertension as well as diabetes mellitus (HD), it became necessary to evaluate the separate effects of both diseases on the heart. Accordingly, we selected three approximately age-matched control groups from autopsies performed by the anatomic pathology service of the Bronx Municipal Hospital Center.

The diabetic group (D) consisted of five patients who had adult onset diabetes mellitus

Table 1 Hypertensive-diabetic cardiomyopathy. Clinical summary

Case no	Age/ sex/race	Duration of DM (years)	DM treatment	Blood pressure	CHF	AKW	Other finding	Cause
1	63/M/B	34	Insulin	Shock, Hx $\uparrow$ BP	+	+	S/P BK amputation	DM con
2	47/F/B	7	Diabenase	200/90	+	+	S/P BK amputation	CHF
3	41/F/B	10	In.ulin	170/100	+	+	S/P BK amputation	DM con
4	58/M/B	-	In.ulin	160/96	+	+	S/P BK amputation	CHF
5	70/M/W	20-25	In.ulin	160/80	+	-	S/P cholecystectomy	Acute n
6	67/M/W	20	Insulin	Shock, Hx $\uparrow$ BP	+	+	GI hemorrhage	GI hem
7	46/M/B	20	Insulin	160/96	+	+	Renal failure	Uremia
8	70 F/W	10	Diabenase	300/190	+	-	Bronchopneumonia	Bronch
9	63/M/W	11	In.ulin	Hx $\uparrow$ BP	+	+	S/P BK, AK amputation	Bronch

Abbreviation. DM = diabetes mellitus CHF = congestive heart failure AKW = Kimmelstiel-Wilson disease

with no clinical or pathological evidence of hypertension. The duration of disease, the levels of hyperglycemia, and the form of treatment were comparable to the HD group. The hypertensive group (H) comprised five patients with hypertension as defined above but with no diabetes mellitus. The levels of systolic and diastolic blood pressure were comparable to those in the HD patients. The normal group (N) was composed of five patients who died of non cardiac disease with no clinical or pathological evidence of diabetes mellitus or hypertension. None of the patients in the three control groups had large coronary artery disease involving more than 50% of the luminal diameter. The smaller size of the control groups compared to the HD study group was a result of difficulty in identifying normotensive diabetics or of finding either hypertensive or normal patients without significant coronary atherosclerosis in the age range required by this study.

Statistical comparison of the four groups was performed by means of the Mann-Whitney non-parametric test and Student's *t* test where appropriate. A *p* value less than 0.05 was considered statistically significant.

## Results

**Clinical findings (see Table 1).** The hypertensive-diabetic group (HD) was composed of three women and six men. The mean age was 58.4 years. Six of the nine had been diabetic for more than 10 years (mean for the entire group 9 years). Two patients were treated with diet alone while seven were insulin-dependent. Six patients were hypertensive on admission to the hospital while three

were in shock but had a history of hypertension. Of interest, despite the fact that nine patients had no evidence of occlusive coronary artery disease at autopsy, peripheral vascular disease necessitated extremity amputation. Two patients had a clinical diagnosis of an acute myocardial infarction prior to their terminal hospitalization, although postmortem examination revealed evidence of an old infarction. Seven patients had the clinical diagnosis of diabetic glomerulonephritis, although only one patient had azotemia and proteinuria. Kimmelstiel-Wilson disease (nodular glomerulosclerosis) was confirmed pathologically in these seven patients. Nine HD patients had long-standing evidence of congestive heart failure requiring cardiac therapy.

The diabetic group (D) was composed of four men and three women with a mean age of 58.2 years. Four patients in this group were dependent on insulin. No patient had a blood pressure recording higher than 130/75 mm Hg. There was no evidence of congestive heart failure. One patient had Kimmelstiel-Wilson disease. Although the group is small, it may be noted that the relative infrequency of nodular glomerulosclerosis in this normotensive series of patients with long-standing diabetes mellitus contrasts with the direct result of their diabetes mellitus while one died of chronic pyelonephritis and two died of malignancy.

The hypertensive group (H) was composed of two men and three women with a mean age of 58.2 years. None had a history of congestive heart failure, although one patient had



Fig. 1 This horizontal section of left and right ventricle from Case No. 6 demonstrates marked biventricular hypertrophy. The left ventricular wall has a diffuse paleiness secondary to extensive interstitial connective tissue deposition. The coronary artery (thick arrow) is widely patent. Several focal dark areas, which are particularly well seen in the papillary muscle (thin arrow) represent zones of recent myocardial infarction.

Table II Hypertensive diabetic cardiomyopathy: pathological

Case no.	Heart weight (gms.)	Th. line (cm)		Scars	Interstitial fibrous	FAS (+)	Myocardial infarction	P.V.F.	V.C.
		LV	RV						
1	310	1.8	0.5	3+	3+	2+	2+	1.6	1.1
2	420	1.6	0.3	2+	2+	2+	—	1.2	0.8
3	310	0	1.0	3+	2+	2+	—	2.3	1.3
4	400	1.6	0.4	2+	4+	2+	1+	3.9	1.4
5	480	1.6	0.5	3+	4+	3+	1+	5.4	2.9
6	620	1.9	0.5	2+	4+	3+	3+	4.4	2.3
7	450	1.0	0.5	2+	4+	1+	1+	2.1	0.7
8	600	1.5	0.6	3+	4+	3+	1+	4.0	3.4
9	490	1.5	1.0	1+	3+	+	1+	3.1	0.8
Mean	454	1.8	0.6	2.4+	3.4+	2.2+	1.1+	3.6	1.5

Abbreviations: P.V.F. = perivascular fibrosis; V.C. = vascular changes; M.I. = myocardial infarction.

failure following a subarachnoid hemorrhage. Blood pressures ranged from 170/110 to 260/110 mm Hg. Four patients died of acute subarachnoid or intracerebral hemorrhage while one patient succumbed to chronic renal failure secondary to multiple myeloma.

The normal group (N) was composed of five women with a mean age of 51.5 years. There was no history of hypertension, diabetes mellitus, nor congestive heart failure. The causes of death included extensive burn, septic shock, metastatic carcinoma (two) and massive upper gastrointestinal

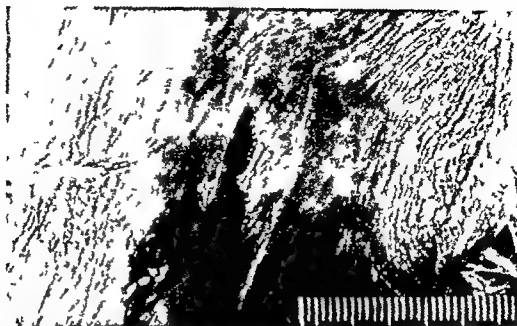


Fig. 2 This view of the sectioned ventricular septum from Case No. 5 reveals a large zone of myocytolysis, with characteristic depressed, hemorrhagic, and semitranslucent appearance. Surrounding this area are several foci of fibrosis.

Table III Comparative pathology: Hypertensive diabetics versus controls

Group (number)	Heart weight (gm)	Score (grade)	Interstitial fibrosis (grade)	Myocytolysis (grade)	PVF*	IS
Normal (5)	165 ± 69	0.4	0.6	0.4	20 ± 10	14 ± 0.6
Diabetic (5)	149 ± 60	0.4	0.4	0	40 ± 0.7	13 ± 0.1
Hypertensive (5)	134 ± 9	1.4	1.6	0	34 ± 1.4	12 ± 0.6
Hypertensive-diabetic (9)	172 ± 105	2.4	3.1	1.1	36 ± 1.6	15 ± 1.0
Comparison	HD vs H D p < 0.01 N p < 0.01	HD vs H D p < 0.005 D p < 0.001 N p < 0.001	HD vs H D p < 0.001 D p < 0.001 N p < 0.001	HD vs H D p < 0.001 D p < 0.001 N p < 0.001	HD vs H D vs N NS	HD vs H D vs N NS

Note 1. All figures represent mean, with standard deviations calculated for the numerical determinations (Heart weight, PVF %).

Note 2. Statistical analysis of the numerical data was by means of Student's *t* test; that for the graded determinations was by means of the Mann-Whitney nonparametric test.

Note 3. PVF = pericardial effusion; IS = interstitial fibrosis.

Mean weight = 172 gm.

terminal hemorrhage in a patient with adenocarcinoma of the endometrium.

#### Pathological findings (see Tables II and III)

**Macroscopic observations.** The HD hearts had the characteristic gross appearance (Fig. 1). There was marked concentric left ventricular hypertrophy with an overall heart weight of  $129 \pm 105$  grams (mean  $\pm$  SD). This compared with heart

weights of  $134 \pm 97$  grams in the H group,  $149 \pm 68$  grams in the D group, and  $165 \pm 69$  grams in the N group. The blood pressure range of the HD and H patients was comparable. Two major changes were noted in the HD hearts in comparison with the three other groups. The HD hearts had a firm, almost waxy consistency, resembling the consistency of hearts with diffuse interstitial amyloidosis (amyloid stain were

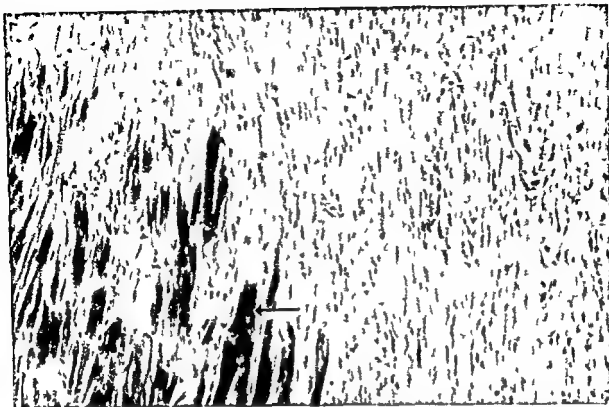


Fig 3 A focal scar from Case No. 7 is densely collagenized but the appearance of the tissue is suggestive of a healed myocytolytic zone. Supporting this interpretation, the residual myocardial fibers in the area are undergoing contraction band necrosis (arrow). In other histological sections from the nine cases, the evolution of these focal scars could be clearly traced from stages of acute myocytolysis through early collagen deposition (see Fig 10) to finally dense fibrosis (Trichrome stain, original magnification  $\times 200$ ).

negative in all nine cases). This firmness was probably a result of extensive connective tissue and associated PAS positive glycoprotein deposition in the HD hearts (*vide infra*). The firm waxy quality of the myocardium was not appreciated in any of the three control groups, even in the comparably hypertrophied H hearts. The other characteristic alteration was the frequency of depressed hemorrhagic semi-translucent focal lesions in the HD hearts (Fig 2). These areas were most commonly noted in the subendocardial and midwall myocardium. Histology of these zones revealed the presence of active and healing myocytolysis.

Small focal areas of gross scarring were commonly observed in the HD hearts, rarely in the H hearts, and not at all in the other two groups. The left ventricular wall thickness was greater than 1.5 cm in all nine HD hearts and in four of five H hearts, while it was normal in the other controls. Right ventricular wall thickness was greater than 0.5 cm in three of nine HD, one of five H, and

none of five D and N hearts. Extramural coronary artery atherosclerosis did not compromise the lumen of any vessel by more than 40% in any of the four groups.

**Microscopic observations.** Focal myocardial scars were common in the nine HD hearts (Fig 3, Tables II and III). Transitional zones of scar formation were observed in areas of myocytolysis and it is presumed that the healing of this latter process results in focal scar lesions. In all but one HD heart scars were graded as either 2+ or 3+ in frequency, whereas in the H hearts they were present to a lesser degree. The differences between the two groups were significant at the 0.05 level. Similar scarring was noted in just two hearts of the D and N groups, and in each of these it was present with only a 1+ frequency.

The most striking microscopic feature of the HD hearts was the distribution of dense interstitial connective tissue throughout the myocardium (Fig 4, Tables II and III). The fibrous tissue frequently surrounded individual or groups of



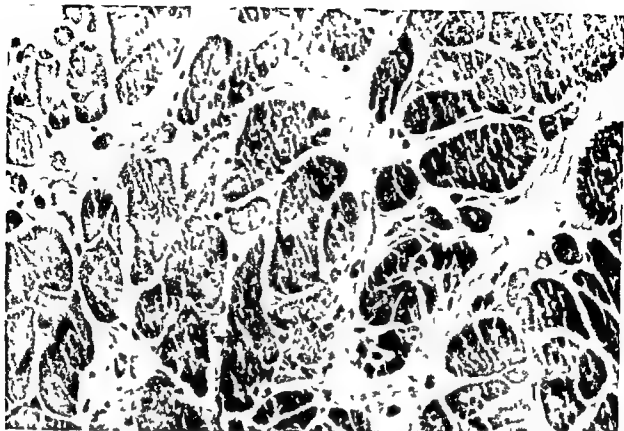


Fig 4 This section of left ventricular myocardium from Case No 2 demonstrates diffuse interstitial fibrosis. There is marked variability of myocardial cell size with virtually every cell surrounded by dense collagen. This abnormality was a characteristic feature of the hypertensive-diabetic hearts (Hematoxylin-eosin original magnification  $\times 250$ ).

muscle cells completely isolating them. There was no obvious relationship between the presence of interstitial connective tissue and abnormalities of vessels in the 50 to 200 micron size range. However, whether such fibrosis was related to alterations of smaller blood vessels could not be ascertained with the light microscope. In all but three HD cases, the interstitial fibrosis had a frequency of 4+ in comparison with mild to moderate (1 to 2+) fibrosis in the H group and minimal (0 to 1+) fibrosis in the D and N groups. The differences between the HD patients and the three other groups were significant at the 0.01 level.

Semiquantitative evaluation of PAS positive diastase-resistant material revealed it to be common in the HD hearts and rare in the three other groups. It was of interest that the material was invariably localized to areas of interstitial fibrosis or scars (Fig 5) and seemingly was absent in areas of normal myocardium. Occasional foci of PAS positivity were observed in fibrotic lesions in the three control groups. Similarly, intramyocar-

dial vessels in all four groups demonstrating vascular sclerosis or perivascular fibrosis had PAS positive material in their walls.

Foci of myocytolysis were observed in all but two hearts from the HD patients (Fig 6, Tables I and III). The frequency varied in the group, however, it was present at a grade of 2+ and 3+ in two cases. In contrast, myocytolysis was not noted in any of the H or D hearts, while grade 1+ was seen in two N controls.

Evaluation of intramyocardial vascular changes revealed surprising semiquantitative results. Although we fully expected significant alterations in the HD hearts, in fact we were unable to detect statistical differences in any of the four groups (Table III). Both perivascular fibrosis and vascular sclerosis (Fig 7) subjectively appeared more severe in the HD and H heart. However, the tabulation of abnormal vessels per square centimeter of tissue examined clearly revealed no statistical differences. Since the comparison was numerical rather than an evaluation of the degree of abnormality in each vessel, the

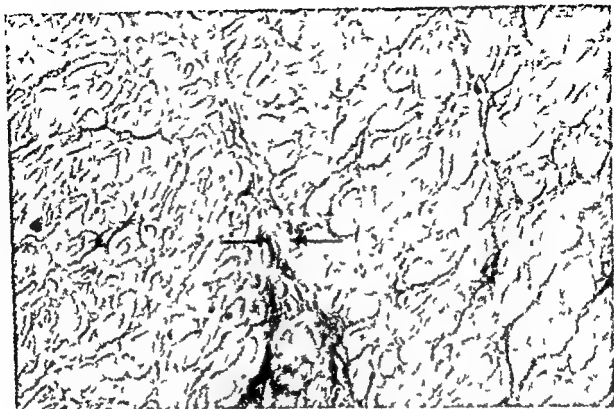


Fig 5 This PAS stained section of left ventricular myocardium reveals PAS positive diastase resistant material predominantly localized to areas of interstitial fibrosis (arrow). Regions of myocardium devoid of pathological connective tissue deposition were equally devoid of PAS positive material. This was a consistent observation in this series of hypertensive diabetic patients. PAS positive material did not diffusely infiltrate the myocardium nor was it observed frequently in the diabetic control group (H&E stain after diastase pretreatment, original magnification  $\times 200$ ).

figures tend to understate the differences between groups. In fact, the vascular abnormalities in the HD and H hearts were more severe qualitatively than in either the D or N hearts.

### Discussion

The cardiovascular complications of diabetes mellitus comprise a significant proportion of the morbidity and mortality of this disease. Although many of these complications result from the effects of atherosclerosis, recent epidemiologic, clinical, and experimental data suggest that there may be a specific cardiomyopathy causing congestive heart failure in the absence of extramural coronary artery atherosclerosis. This diabetic cardiomyopathy has not been well characterized either clinically or pathologically. In particular, interactions between diabetes mellitus and other diseases such as hypertension have not been investigated for their potential causal role in the development of pri-

mary myocardial failure. The present report describes the clinical and postmortem pathological features of nine diabetic patients with congestive cardiomyopathy; the data suggest that hypertension is significantly related to the pathogenesis of severe diabetic heart disease.

Although at least one major study has disputed the increased prevalence of hypertension in the diabetic population, most recent reports have amply documented this association. Christlieb and co-workers, at the Joslin Clinic, have demonstrated that hypertension in the diabetic is usually a consequence of widespread arteriolar hyalineization, increasing peripheral vascular resistance and decreased renal free water clearance, producing a high circulating blood volume. This form of hypertension is commonly hyporenemic and hypoadosteronemic. Of particular relevance, seven out of the nine hypertensive and diabetic patients in our study had histological evidence of renal disease with

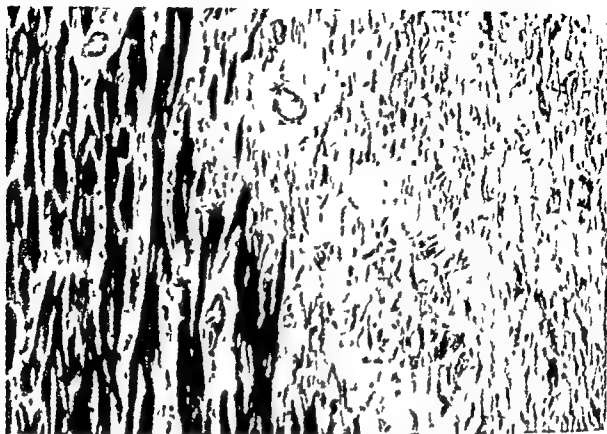


Fig 6 This area of recent myocardial infarction from Case No 5 is characterized by many empty spaces representing sites of myocardial cell dropout, proliferating fibroblasts, chronic inflammatory cells, hemorrhage, and capillaries. Early collagen deposition is occurring within the zone. The residual myocardium is generally well preserved, although the cells are surrounded by interstitial fibrosis (Trichrome stain, original magnification  $\times 200$ ).

typical diabetic lesions of nodular glomerulosclerosis.

Despite frequent statements that hypertension adversely affects the cardiovascular complications of diabetes mellitus,<sup>3</sup> most of the data have been inferential with little objective evidence adduced to support the claims. Christlieb and associates<sup>4</sup> described 28 diabetic patients with hypertension, 27 of whom also had retinopathy; this diabetic complication was much less common in normotensive patients. Oakley and co-workers<sup>5</sup> described a series of long-term diabetic patients followed for more than 40 years who had a striking absence of severe complications and concurrently had a low prevalence of high blood pressure. Mogensen<sup>6</sup> reported a group of patients with diabetic nephropathy in whom the progression of the renal disease was slowed by antihypertensive treatment. In an animal study examining the effects of renal artery clipping on the development of glomerular lesions in hypertensive diabetic rats, Mauer and colleagues<sup>7</sup> showed that the clipped kidneys were

protected from diabetic damage while the clipped kidney exposed to Goldblatt hypertension developed diabetic alterations. Similarly, a case report<sup>8</sup> documented the absence of diabetic glomerulopathy in a hypertensive diabetic patient with unilateral renal artery stenosis, whereas the unprotected kidney had diabetic changes. The present report specifically suggests that hypertension may be causally related to diabetic cardiomyopathy.

The clinical features of the HD patients are remarkably similar. They were mostly longstanding insulin-dependent diabetics with disease. Despite the absence of significant obstructive large coronary artery disease, the patients had severe aortic atherosclerosis, five had peripheral vascular disease, and one had amputation. The reason for the discordance between the coronary and extracardiac vessels is unknown and it requires further study. The patients all had long histories of congestive heart failure, which in most cases was thought to be a consequence of ischemic coronary artery disease.



Fig 7 The intramyocardial artery has a widely patent lumen but the wall of the vessel is locally replaced by collagen and other stains demonstrate PAS-positive material and elastic tissue proliferation. This process is characterized as vascular sclerosis in our semiquantitative analysis. Concentric fibrous cuffs the vessel and impinges on the surrounding myocardium and represents an example of perivascular fibrosis as tabulated in this study. (Trichrome stain, original magnification  $\times 200$ )

Two patients had even been diagnosed as having myocardial infarction, yet we found no pathological evidence of old infarcts at autopsy.

Pathologically, there were several characteristic but non-specific features of HD heart disease. It is important to emphasize that the lesions described in this report are not unique to this group of patients, but are frequently observed in many other types of cardiomyopathy. Employing semiquantitative techniques, however, we were able to differentiate the alterations in hypertensive diabetic hearts from the changes observed in hypertensive, diabetic or normal subjects.

We believe that fibrosis is the most important functional lesion in the HD hearts. Statistical analysis revealed a significant increase of interstitial fibrosis in these hearts compared to the H control group where such lesions were less common, and the D and N groups where it was distinctly rare. It is probable that this fibrosis contributes to the tactile sensation of stiff muscle observed grossly. Although this theory is

speculative, this fibrosis may be sufficient to account for limited ventricular contraction producing clinical cardiomyopathy. The fibrosis also appears to be related to the localization of PAS-positive diastase-resistant material in the myocardium. In contrast to the reports of Regan and associates<sup>10</sup> who found PAS-positive material in human and canine hearts with diabetes mellitus and no apparent hypertension, we observed no pronounced deposition in the diabetic group and only found such material in the regions of interstitial fibrosis and focal scar in the hypertensive diabetic as well as in the hypertensive hearts. The similar localization of PAS-positive glycoprotein and interstitial collagen suggests that the deposition of both substances has a common pathogenesis. It is tempting to propose that they result from increased vascular permeability due to the combination of diabetic and hypertensive injury to small vessels, however, as yet no evidence exists to support this mechanism.

Focal scars were also present to a significant degree in the HD hearts in comparison with the three other groups. These patchy scars were generally microscopic in size, but rarely were large enough to be appreciated macroscopically. They often were scattered haphazardly throughout the myocardium and this fact plus their size mitigated against their being caused by overlooked lesions in the large coronary arteries. In several hearts it was possible to trace the development of scars from myocytolytic foci which progressed from acute through a healing stage of dense collagen deposition. We believe that the frequent observation of myocytolysis in the HD hearts explains the frequency of the focal scars in these patients. It is of interest to note that myocytolysis is a form of myocardial necrosis thought to be secondary to exogenous catecholamine administration or endogenous catecholamine excess.<sup>1</sup> Although long-term diabetics have markedly reduced tissue levels of norepinephrine,<sup>11</sup> those diabetic patients with complications (retinopathy) have increased vascular reactivity to this agent.<sup>12</sup> The role of catecholamines and other vasoactive substances in the initiation of myocardial fibrosis in hypertensive diabetics and its possible involvement in the development of cardiomyopathy require further exploration.

The semiquantitative morphologic analysis in this study demonstrated that there was no significant difference in the numbers of small intramyocardial vessels with abnormalities in any of the four groups of patients. This implies (but in no way is definitive) that small vessel disease is not the cause of hypertensive diabetic cardiomyopathy. However, subjectively it was apparent that the degree of vascular abnormality in any single vessel was more severe in the HD hearts than in the other groups. Thus localized tissue ischemia may still be an important factor in the pathogenesis of this disease.

The finding that severe cardiomyopathy in diabetes mellitus is related to the presence of hypertension was an unexpected result of our study. Initially our objective was to examine a consecutive autopsy series of patients with diabetes mellitus, congestive heart failure, and minimal coronary artery disease. Only in retrospect did it become apparent that all nine patients selected for inclusion were hypertensive. Other studies of diabetic cardiomyopathy have explicitly

excluded hypertensive patients from analysis and therefore this association has probably been overlooked. That hypertension alone can account for the severity of the lesions we observe is confirmed by the quantitative differences between the H and HD groups. Similarly, non-tensive diabetics showed only minimal card changes. The absence of pathological cardiac alterations in patients with long-standing non-tensive diabetes mellitus clearly separates this study from previous reports of diabetic cardiomyopathy. We have no explanation for this discrepancy.

Several potential limitations of the present study should be considered. The differences in mean heart weight between the four groups may provide an alternative explanation for the severity of the degenerative lesions in the hypertensive diabetics. On the other hand, the overlap between heart weights in the HD and H group provides means to evaluate the significance of this parameter. Though the groups are small, a comparison of the heart weights in the HD and H patients well as within the entire HD group (see Table I) suggest that the severity of the lesions does not correlate with heart weight. Obviously, however, this is an important question which will require study of larger numbers of patients. An additional consideration concerns the nature of the control groups employed in this study. Ideally, an appropriate control group for the hypertensive diabetic patients with cardiomyopathy would have been a series of hypertensive patients with similar degrees of congestive heart failure. In search for such a group we were limited by the small numbers of patients without epicardial coronary artery disease who otherwise fulfilled our criteria. Therefore, further studies will be required to establish if hypertensive patients with congestive heart failure have myocardial degeneration similar to hypertensive diabetic individuals with failure.

It may be argued that observer bias or inappropriate controls could account for the differences between our study and others. This would be difficult to refute if we had not had the opportunity to carry out a series of quantitative morphological investigations in an animal model of human disease. We analyzed rats made diabetic with streptozotocin and hypertensive with unilateral renal artery clip and compared the animals with normotensive controls, normotensive

sive diabetics and non diabetic hypertensives. The range of abnormalities occurring within a brief 8 week period was strikingly similar to human HD cardiomyopathy reported herein and established that the combination of hypertension and diabetes mellitus is associated with the development of significant interstitial fibrosis and focal scars. Observations regarding deposition of PAS positive material, myocytolysis and small vessel disease were identical to those described in the present study. These experiments provide preliminary confirmation for our contention that the combination of diabetes mellitus and hypertension produces significant myocardial morphological damage. The similarity of the animal model to the human disease suggests that in the future the rat hypertensive diabetic model will enable us to explore the pathogenesis of this form of cardiomyopathy in more detail.

### Summary

The existence of a specific cardiomyopathy secondary to diabetes mellitus is controversial. During a 2 year period we had the opportunity to examine nine diabetic patients at autopsy who had clinically severe congestive heart failure and minimal extramural coronary artery atherosclerosis. Unexpectedly all nine patients were found to be hypertensive. Accordingly we initiated a detailed study of the clinical and morphological features of this group and compared the findings to age matched autopsied subjects with either isolated hypertension, isolated diabetes mellitus or no heart disease.

The study of the hypertensive diabetic hearts revealed severe interstitial fibrosis, focal or confluent scars and extensive myocytolytic activity. Comparison with the diabetic, hypertensive and normal groups showed statistically significant differences in regard to the degree of interstitial and focal scarring and the presence of myocytolysis. Only the hypertensive group had minimal interstitial scarring. There were no statistical differences in the small vessel changes between the four groups, although subjectively the hypertensive and hypertensive diabetic patients had more severe disease.

It is concluded that the association of diabetes mellitus and hypertension in the absence of significant coronary artery atherosclerosis may lead to a severe cardiomyopathy. Although the etiology of myocardial failure in this syndrome is

uncertain, the degree of myocardial fibrosis and the frequency of myocytolytic lesions possibly related to catecholamine hypersensitivity are potential explanations. Several studies suggesting that hypertension has adverse consequences in diabetes as well as an animal model of hypertensive diabetic cardiomyopathy support our conclusion that cardiomyopathy associated with diabetes mellitus is a specific entity which may be secondary to the combined effects of diabetes and hypertension on the myocardium.

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## Technetium 99m stannous pyrophosphate myocardial scintigrams in pericardial disease\*

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Previous studies in experimental animals and man have demonstrated that  $^{99m}\text{Tc}$  PYP myocardial scintigraphy is a very sensitive technique for diagnosing acute myocardial infarction.<sup>1-3</sup> However recent reports indicate that abnormal myocardial scintigrams may occur in clinical conditions other than acute myocardial infarction such as ventricular aneurysm,<sup>4</sup> stable and unstable angina pectoris,<sup>5</sup> old myocardial infarction,<sup>6</sup> slow ongoing myocardial necrosis,<sup>7</sup> following high energy transthoracic cardioversion,<sup>8</sup> metastatic disease of the heart,<sup>9</sup> myocardial contusion,<sup>10</sup> myocardiopathy,<sup>11</sup> valvular calcification,<sup>12</sup> experimental endocarditis,<sup>13</sup> and even in apparently normal hearts.<sup>14</sup>

Since acute pericarditis may mimic many of the

clinical features of acute myocardial infarction including chest pain, nonspecific electrocardiographic changes and transient serum enzyme abnormalities the present investigation was undertaken to assess  $^{99m}\text{Tc}$  PYP myocardial scintigraphy in patients with acute and chronic pericardial disease. The results from this study are reported here.

### Methods

The study population consisted of 38 patients, 35 with acute pericarditis and three with chronic constrictive pericarditis. All the patients were males ranging in age from 22 to 67 years (mean 48 years). Acute pericarditis was diagnosed by typical history and the presence of a two or three component pericardial friction rub. Chronic constrictive pericarditis was diagnosed by history, physical examination and findings at cardiac catheterization. None of the patients had unstable angina pectoris, recent high energy transthoracic cardioversion, a calcified cardiac valve or were in congestive heart failure. Seven of the patients had a documented myocardial infarction five or more weeks prior to scintigraphy. To differentiate a positive scintigram related to acute pericarditis from a persistently positive scintigram due to myocardial infarction a negative follow up scintigram was required in all patients with prior myocardial infarction and a positive scintigram during acute pericarditis.

Technetium 99m myocardial scintigrams were obtained in all 35 patients with acute pericarditis 30  $\pm$  12 days after the onset of symptoms or the

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Table 1 Etiologies of acute and chronic pericarditis and interpretation of myocardial scintigrams

Etiologic diagnosis	Number of patients	Positive scan (no)	Positive scan (%)
Acute pericarditis	35	13	37
Idiopathic	11	6	55
Viral	1	0	0
Bacterial	2	1	50
Tuberculosis	1	1	100
Connective tissue disease	3	0	0
Uremia	5	0	0
Postmyocardial infarction syndrome	6	2	33
Metastatic neoplasm	4	1	25
Unrecognized myocardial infarction	1	1	100
Post thoracotomy syndrome	1	1	100
Chronic constrictive pericarditis	3	1	33
Idiopathic calcific	1	1	100
Idiopathic noncalcific	1	0	0
Post traumatic	1	0	0

Table 2 Characteristics of  $^{99m}\text{Tc}$  PYP myocardial scintigrams obtained in 35 patients with acute pericarditis

Number of patients	R	R	D	D	D	n
35	1	5	0	7	9	33

Abbreviations: R = regional 3+ activity; R = regional 2+ activity; D = diffuse 3+ activity; D = diffuse 2+ activity; D = diffuse 1+ activity; 0 = no activity; - = negative scintigram.

appearance of their pericardial friction rub and one day prior to cardiac catheterization in the three patients with chronic constrictive pericarditis. Eight of the 35 acute pericarditis patients (23%) and one of the three chronic constrictive pericarditis patients (33%) had a follow-up scintigram 6.1  $\pm$  2.3 weeks after their initial study.

Myocardial imaging was performed two hours after the injection of 20 mCi of  $^{99m}\text{Tc}$  PYP containing less than 0.15 mg of tin. Chromatography as previously described was performed prior to each study. In all studies free technetium was less than 1% and reduced hydrolyzed technetium was less than 0.1%. Repeat imaging at four hours after injection was performed in all patients with suspected persistent blood pool activity. Myocardial images were obtained in three views: left anterior 45 degree, left anterior oblique, and left lateral projections. Myocardial scintigrams were recorded using either a Scarcie Pho Gamma HP scintillation camera with a Divicon collimator in the converging mode or a Scarcie Pho Gamma V

scintillation camera with a high resolution collimator. Each view contained 500,000 counts with the Divicon collimator or 400,000 counts with the high resolution collimator with a 20% window and a photo peak centered on 140 keV. Serial studies on individual patients were performed by the same camera and collimator.

The myocardial scintigrams were interpreted using our grading system. Zero activity indicated no myocardial activity. An intensity of 1+ was assigned for myocardial activity less than that of the ribs 2+ for activity equal to or greater than rib activity and 3+ for activity equal to or greater than sternal activity. A scintigram of 3+ or greater activity was considered abnormal. Using this grading system of 361 patients with documented acute myocardial infarction treated at our hospital, 331 (92%) had positive scintigrams obtained during their infarction while one of 46 patients (2%) without clinical heart disease had a positive scintigram.

Myocardial scintigrams were graded according to the distribution of activity. Regional uptake was considered when activity was localized to an anatomical wall of the heart. Diffuse uptake was assigned when anatomical location was indeterminate. Myocardial scintigrams were interpreted by two independent observers without knowledge of the patients' diagnosis or clinical status. There was complete agreement between the two observers in all the myocardial scintigrams interpreted.

During their hospitalization all 35 patients

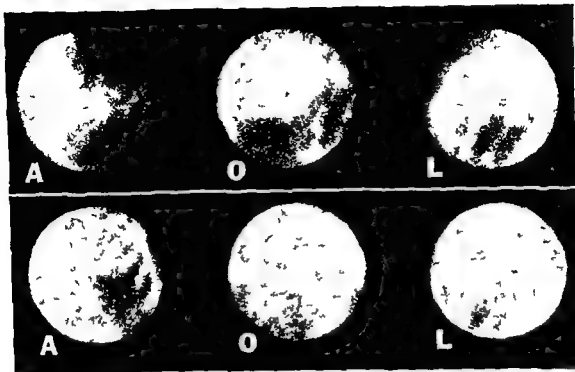


Fig 1 The upper panel shows a positive myocardial scintigram with a 3+ regional abnormality in a patient with postmyocardial infarction pericarditis. The patient had an uncomplicated myocardial infarction 5 weeks prior to the onset of acute pericarditis. The lower panel shows a negative follow up myocardial scintigram 6 weeks after acute pericarditis. A = anterior O = 45 degrees left anterior oblique L = left lateral projections

with acute pericarditis had serial 12 lead electrocardiograms blood analyzed for serum enzymes CK CK MB SGOT LDH and HBD and echocardiograms. Diagnosis of acute pericarditis by electrocardiography was considered certain if there was diffuse concave ST segment elevation in epicardial leads followed by evolutionary ST T wave changes without development of new Q waves. Pericardial effusion was diagnosed by echocardiography or by pericardicentesis.

The data are presented as the mean  $\pm$  the standard deviation. The chi square test was used to test for significant differences.

## Results

**Scintigraphic findings in acute pericarditis**  
The etiologies of the acute pericarditis and the interpretation of the myocardial scintigrams are shown in Table I. Of the 13 patients with positive scintigrams six (46%) had a regional abnormality and seven (54%) had a diffuse abnormality (Table II). One patient had a 3+ intensity myocardial scintigram.

Fig 1 illustrates a positive myocardial scintigram with a regional abnormality in a patient

with postmyocardial infarction pericarditis. The patient had an uncomplicated myocardial infarction 5 weeks prior to onset of acute pericarditis. The lower panel shows a negative follow up scintigram in this patient 6 weeks after acute pericarditis. Fig 2 illustrates a diffuse scintigraphic abnormality during acute idiopathic pericarditis.

Table III correlates the electrocardiographic features elevation of CK elevation of CK plus CK MB serum enzymes and the presence or absence of pericardial effusion with the incidence of positive scintigrams during acute pericarditis. As indicated patients with acute pericarditis and classic electrocardiographic changes of acute pericarditis were significantly more likely to have positive myocardial scintigrams compared to patients without these electrocardiographic changes. Two patients had transient atrial fibrillation during acute pericarditis and both had positive myocardial scintigrams.

Of the eight patients with acute pericarditis who had follow up scintigraphy all five patients with initially positive studies had negative studies at follow up  $62 \pm 13$  weeks after initial scintigraphy (Fig 1). Of the three patients who had



Fig 2 A positive myocardial scintigram with a 2+ diffuse abnormality in a patient with acute idiopathic pericarditis A = anterior O = 45 degree left anterior oblique L = left lateral projections

Table III Electrocardiographic features CK and CK MB elevation and presence or absence of pericardial effusion correlated with the results of myocardial scintigraphy in 35 patients with acute pericarditis

Parameter	Number of patients	Positive scan	
		No	%
Electrocardiogram			
Consistent with acute pericarditis	18	10	56
Not consistent with acute pericarditis	17	3	18
Acute inferior infarction	1	1	100
Old anterior infarction	2	0	0
Old inferior infarction	3	1	33
Left ventricular hypertrophy	3	1	33
RBBB and LAH	1	0	0
Low voltage and nonspecific ST T wave changes	1	0	0
Non specific ST T wave changes	7	0	0
CK			
CK elevation	3	4	67
CK plus CK MB elevation	2	2	100
Pericardial effusion			
Present	27	8	30
Absent	8	0	0

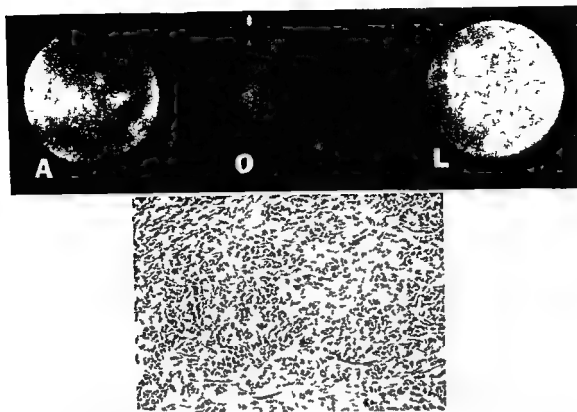
Abbreviations: RBBB = right bundle branch block LAH = left anterior hemiblock % = P < 0.05 compared with ECG not consistent with acute pericarditis

initially negative scintigrams all three had negative studies at follow up  $60 \pm 21$  weeks after initial scintigraphy

Autopsy data were obtained in one patient with malignant pericarditis secondary to bronchogenic carcinoma of the lung Fig 1 shows the myocardial scintigram obtained in this patient during acute pericarditis and a histologic section of his myocardium obtained at autopsy one month later The tumor involved not only the parietal

pericardium but also involved extensive areas of both the right and left ventricles

Scintigraphic findings in chronic constrictive pericarditis The etiologic basis of the patients' chronic constrictive pericarditis and the results of the myocardial scintigrams are shown in Table I Only one patient with chronic constrictive pericarditis had an abnormal scintigram This patient had pericardial calcification determined by image intensification at cardiac catheterization and by



**Fig 3** The upper panel shows a 2+ positive myocardial scintigram in a patient with acute malignant pericarditis from metastatic bronchogenic carcinoma. The lower panel shows a histologic section of left ventricular myocardium from this patient. The normal architecture of the myocardium is completely disrupted by large sheets of malignant cells showing extreme variation of size and shape. There is interstitial edema, fibrosis and varying degrees of myocardial necrosis (Hematoxylin and eosin stain, original magnification  $\times 100$ ).

histologic sections of pericardium removed at surgery. Fig 4 shows serial myocardial scintigrams and a histologic section of pericardium removed at surgery in this patient. The other two patients with negative myocardial scintigrams had only thickened noncalcific fibrotic pericardium removed at surgery.

### Discussion

The results from the present study indicate that  $^{99m}\text{Tc}$  PYP myocardial scintigrams obtained in patients with acute pericarditis or chronic constrictive pericarditis may be abnormal. Thirteen of 35 patients (37%) with acute pericarditis and one of three patients (33%) with chronic constrictive pericarditis had positive scintigrams. The scintigraphic abnormality observed was generally a 2+ regional or diffuse pattern which is similar to that reported in patients with acute nontransmural myocardial infarction.<sup>10</sup> One

patient had a myocardial scintigram which was interpreted as acute transmural inferior wall myocardial infarction. Thus false positive scintigrams for myocardial infarction may occur in patients with pericardial disease.

Traditionally acute pericarditis has been considered an inflammation of the parietal layer of the pericardium, epicardium or both with the formation of exudates within the pericardial cavity. The exudates have been classified as fibrinous, serous, purulent, hemorrhagic and cholesterol.<sup>24</sup> The extent of inflammation and the nature of the exudates are determined by the etiologic agent. With healing there is reabsorption of the exudates and return of the pericardium or epicardium to normal structure.<sup>24</sup> In some patients inflammation continues and there is organization of the exudate with fusion of the parietal and visceral layers of the pericardium. The pericardium may become diffusely thickened

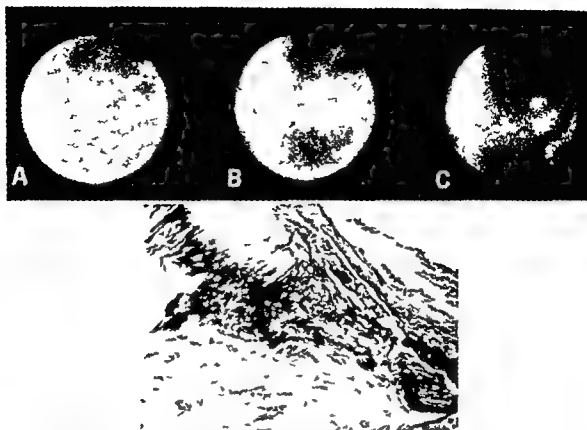


Fig 4 Serial myocardial scintigrams in the patient with chronic constrictive pericarditis and a histologic section of his pericardium removed at surgery. The upper panel shows A Preoperative 2+ positive myocardial scintigram B 3+ positive myocardial scintigram obtained 5 days after pericardiectomy consistent with the clinical diagnosis of a perioperative myocardial infarction and C a 1+ negative myocardial scintigram at follow up 6 weeks after pericardiectomy. The lower panel shows calcification of the parietal pericardium. Dark calcium spicules stand out sharply in contrast to the lightly staining fibrotic pericardium (Hematoxylin and eosin stain original magnification  $\times 10$ )

and fibrotic. Similar changes may occur in the epicardium. These changes may result in cardiac constriction. Calcification of the pericardium may be a late manifestation of the inflammatory process.

The mechanism for positive scintigrams in our patients with pericardial disease is only speculative. In experimental acute myocardial infarction  $^{99m}\text{Tc}$  PYP has been shown to accumulate within the zone of infarction within 12 hours after the onset of injury, reaching a peak within 72 hours and then gradually resolving. Whether the radionuclide combines with soluble or insoluble forms of tissue calcium, which increases during acute infarction, or to macromolecules of denatured protein remains controversial. The importance of the amount of necrotic tissue and delivery of the radionuclide by blood flow to the zone of injury for scintigraphic detection of myo-

cardial necrosis have previously been emphasized.<sup>11,12</sup> Finally, convincing experiments indicate that myocardial uptake of  $^{99m}\text{Tc}$  is always associated with histologic evidence of myocardial necrosis.<sup>13,14</sup>

Thus, it is reasonable to suggest several possible mechanisms for abnormal scintigrams in patients with pericardial disease. These mechanisms include radionuclide accumulation within the pericardium, sequestration of the radionuclide within the exudative process within the pericardial cavity, and myocardial uptake.

The data suggest that pericardial uptake of radionuclide was operative in the patient with chronic calcific pericarditis, while myocardial uptake was the major determinant for positive scintigraphy in patients with acute pericarditis. Of the three patients with chronic constrictive pericarditis, a positive scintigram occurred only

the patient with a calcified pericardium. Further more pericardiotomy resulted in normalization of this patient's scintigram (Fig 4). Thus the presence of calcium within the pericardium most likely concentrated the bone seeking radionuclide and was probably responsible for the abnormal scintigram.

The incidence of myocardial involvement in myocarditis in the clinical setting of acute pericarditis is unknown. Certainly the etiology of acute pericarditis is an important determinant of myocardial involvement. For example studies indicate that myocarditis is not uncommon in viral Coxsackie B pericarditis.<sup>1</sup> Criteria for the clinical diagnosis of myocarditis in the setting of acute pericarditis include ventricular failure manifested by ventricular dilatation, new cardiac rhythm or conduction disturbances, presence of cardiospecific serum enzymes as CK-MB or the presence of distinctive evolutionary electrocardiographic changes of acute pericarditis which most likely represent superficial myocarditis.<sup>2</sup> None of our patients had ventricular failure. The two patients with transient atrial fibrillation and the two other patients with CK plus CK-MB serum enzyme elevation had positive myocardial scintigrams. Of the 13 patients with positive myocardial scintigrams during acute pericarditis, ten (77%) had classical evolutionary electrocardiograms of acute pericarditis. Additionally the positive scintigram in the patient with unrecognized myocardial infarction probably represented accumulation of the isotope in the area of infarction. The one patient with proven myocardial involvement with carcinoma also had a positive scintigram. Other investigators have also noted positive myocardial scintigrams in patients with invasive carcinoma of the myocardium. Although the data suggest that abnormal scintigrams during acute pericarditis are due predominantly to radionuclide sequestration in concomitantly involved myocardium, the contribution of radionuclide accumulation within the involved pericardium and associated exudate will require further study.

Abnormal myocardial scintigrams in normal hearts have been previously reported.<sup>3</sup> Generally, the scintigraphic abnormality is a diffuse pattern rather than a regional pattern. In our experience this scintigraphic abnormality in normal hearts is due to blood pool activity which is the result of

poor preparation of the radiopharmaceutical (excessive tin free or reduced hydrolyzed technetium) or delayed clearance of the radionuclide. Documentation of binding of <sup>99m</sup>Tc PYP prior to each study by chromatography, delayed imaging to four hours after injection and comparison with blood pool studies in the same patients eliminate confusion with regard to false positive blood pool scans.<sup>4</sup>

Serial studies of the eight patients with acute pericarditis and one patient with chronic constrictive pericarditis support the concept that the abnormal images observed in this study represent evidence of pathological involvement of both the pericardium and myocardium. At follow up all five patients with abnormal scintigraphy during acute pericarditis (three diffuse pattern and two regional pattern) were negative. Similarly all three patients with initial negative studies had negative follow up studies. The one chronic constrictive pericarditis patient with an abnormal scintigram had a negative scintigram following pericardiectomy.

Acute pericarditis is traditionally diagnosed by the presence of chest pain, pericardial friction rub and electrocardiographic changes. The true incidence of this disorder is unknown since many patients may not have a pericardial friction rub or electrocardiographic changes. It is possible that some patients admitted to coronary care units with chest pain mimicking acute myocardial infarction who have positive <sup>99m</sup>Tc PYP myocardial scintigrams may have unsuspected acute pericarditis. Thus one must rule out the diagnosis of acute pericarditis in patients with positive <sup>99m</sup>Tc PYP myocardial scintigrams before concluding that an acute myocardial infarction is present.

## Summary

Technetium 99m stannous pyrophosphate (<sup>99m</sup>Tc PYP) myocardial scintigrams were obtained in 35 acute pericarditis and in three chronic constrictive pericarditis patients. Thirteen of 35 acute pericarditis patients (37%) and one of three chronic constrictive pericarditis patients (33%) had abnormal scintigrams (a diffuse pattern in eight patients and a regional pattern in six patients). Of the 17 acute pericarditis patients with classic ST segment changes of acute pericarditis, 10 (56%) had abnormal scinti-

grams compared to three of 17 patients (18%) without these ECG changes ( $P < 0.02$ ). These data indicate that pericardial disease may cause an abnormal scintigram. Therefore one must rule out pericardial disease before concluding that a positive scintigram is due to acute myocardial infarction.

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# Intravenous quinidine pharmacokinetic properties and effects on left ventricular performance in humans\*

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The antiarrhythmic properties of quinidine are well established but its effects on cardiac function are controversial. In vitro studies suggest that quinidine reduces cardiac contractility<sup>1,2</sup> but experiments in conscious, unsedated dogs demonstrate no change in contractility.<sup>3</sup> Although the clinical use of intravenous quinidine has traditionally been considered hazardous, studies from our laboratory<sup>4</sup> and elsewhere<sup>5</sup> indicate that well controlled and monitored intravenous infusions of therapeutic doses can be administered without important untoward effects. The present study assessed the effects of a single intravenous dose of quinidine upon cardiac function in healthy humans as determined by echocardiography. We also investigated the relation of the pharmacodynamic effects of quinidine to its pharmacokinetic properties.

## Methods

**Quinidine administration** Ten healthy volunteers aged 23 to 34 years (eight male, two female) participated in the study after giving informed consent. They were free of identifiable medical disease.

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After a baseline echocardiogram, blood pressure and electrocardiogram (ECG) were obtained, 300 mg of quinidine base (as the gluconate salt\*) was infused into an antecubital vein at a constant rate infusion pump† over 15 minutes with subjects in the supine position. Venous blood samples were taken from the contralateral forearm before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 8, 10, 12, 24, and 36 hours after the start of infusion. Serum was separated and frozen until the time of assay.

The echocardiogram, ECG, blood pressure, and carotid pulse curves were taken with subjects in the supine position at times indicated above at 5 and 10 minutes after the start of the infusion. Subjects remained supine until 45 minutes after the termination of infusion, following which they resumed normal activities. Subsequent physiologic measurements were taken after a 5 to 10 minute rest in the supine position.

**Recording techniques** Echocardiograms were recorded on light sensitive paper using a strip chart recorder‡ (paper speed 50 and 100 mm/sec) and a Picker Echoview 80 20A ultrasound scope§. The ultrasound transducer 2.25 MHz, 127 cm, focused at 75 cm, with a repetition rate of 1000 impulses/sec, was placed parasternally at the third or fourth left intercostal space and directed posteriorly, slightly laterally and inferiorly until the interventricular septum chord.

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‡Hewlett-Packard.

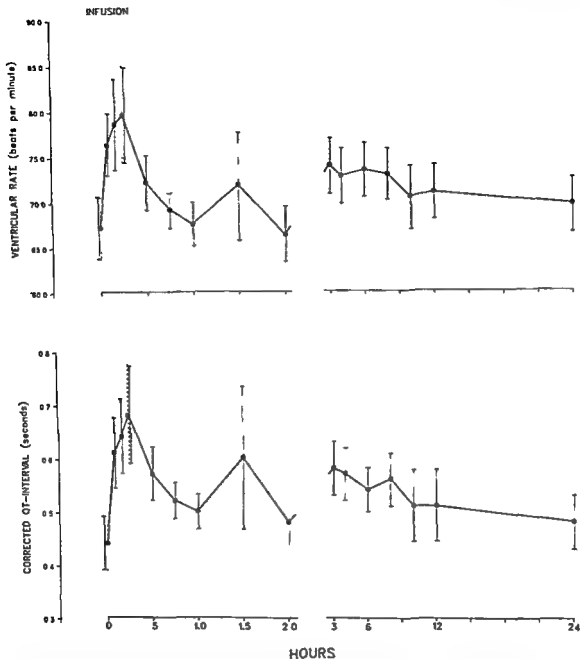


Fig 1 Electrocardiographically determined ventricular rate and corrected QT interval measured before during and after intravenous infusion of quinidine. Each point is the mean ( $\pm$ SE) for all subjects at the corresponding time. The 15 minute infusion (vertical dashed lines) began at time zero.

tendinae of the mitral valve apparatus and the posterior wall were located. The electrocardiogram and the carotid pulse tracing were recorded simultaneously.

Measurement of end systolic cavity dimensions ( $D_s$ ) and diastolic cavity dimensions ( $D_d$ ) were taken from the echocardiogram. End systole was defined as the smallest distance between the

posterior wall and interventricular septum and end diastole was defined as the distance between those two surfaces at the time of onset of the QRS complex.

Ejection time (ET) was determined using the simultaneously recorded carotid pulse tracing. The width of the QRS complex and heart rate were measured on the ECG. If a U wave

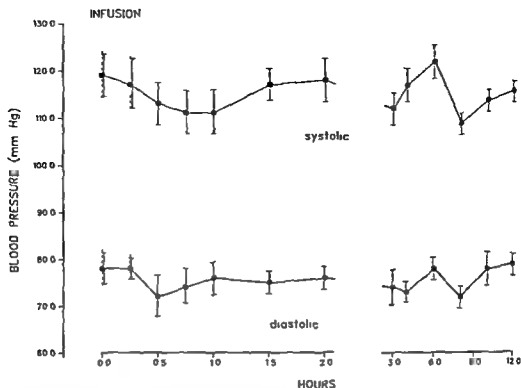


Fig 2 Systolic and diastolic blood pressure measured by cuff sphygmomanometer measured before and after intravenous infusion of quinidine. Each point is the mean ( $\pm$  SE) for all subjects at the corresponding time. The 15 minute infusion (vertical dashed lines) began at time zero.

occurred the maximum downslope of the T wave was extrapolated to the isoelectric line. Blood pressure was measured by a cuff sphygmomanometer.

The following calculations were used as indices of ventricular performance: mean rate of circumferential fiber shortening

$$V_f = \frac{(D_s - D)}{(D_s \times ET)}$$

ejection fraction

$$EF = \frac{(D_s)^2 - (D)^2}{(D_s)^2}$$

**Determination of total and unbound quinidine.** Concentrations of quinidine in body fluids were determined by spectrophotofluorometric assay, the sensitivity and specificity of which are discussed elsewhere. The extent of quinidine binding to plasma protein was determined by equilibrium dialysis.

**Pharmacokinetic and statistical analysis.** The time course of total and unbound serum quinidine concentrations after intravenous infusion were analyzed by computer using weighted nonlinear least squares regression analysis. Data

points for each subject were fitted to a biexponential function of the form

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where  $C$  is the serum quinidine concentration  $t$  after the end of the infusion.  $A$  and  $B$  are hybrid intercept terms and the exponents  $\alpha$  and  $\beta$  are hybrid rate constants. After correction for the infusion period, the fitted function were used to calculate the following pharmacokinetic variables: volume of the central compartment ( $V_1$ ), total volume of distribution, apparent distribution half-life ( $t_{1/2\alpha}$ ), apparent elimination half-life ( $t_{1/2\beta}$ ), and total clearance.<sup>11,15</sup>

The relation of changes in pharmacodynamic variables measured at 0.25, 0.5, 0.75, and 1.0 h after the start of the infusion to total unbound serum quinidine levels determined by the corresponding times was assessed by linear regression analysis.

## Results

### Pharmacodynamics

**Subjective effects.** Two subjects noted no congestion developing during the quinidine infusion. No other subjective changes were reported.

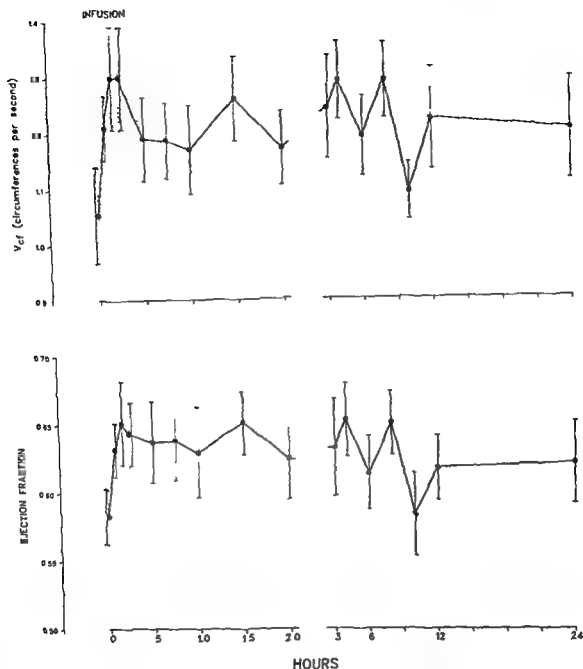


Fig 3 Echocardiographically determined mean rate of circumferential fiber shortening ( $V_{cf}$ ) and ejection fraction measured before, during and after intravenous infusion of quinidine. Each point is the mean ( $\pm$ SE) for all subjects at the corresponding time. The 15-minute infusion (vertical dashed lines) began at time zero.

**Electrocardiographic effects.** Intravenous quinidine produced a transient increase in heart rate and prolongation of the corrected QT interval (QTc) (Fig 1). These changes reverted to or near the pretreatment baseline level following termination of the infusion (Fig 1). No significant changes occurred in QRS duration.

**Cardiac function.** Intravenous quinidine produced no significant changes in blood pressure

(Fig 2).  $V_{cf}$  and EF did not decrease but rather increased significantly over baseline during the quinidine infusion (Figs 3 and 4). These changes reverted partially toward the pretreatment condition shortly after the termination of the infusion. However, considerable variation in these measures was observed over time during the 24 hours after the termination of the infusion.

**Pharmacokinetics.** Table I summarizes phar

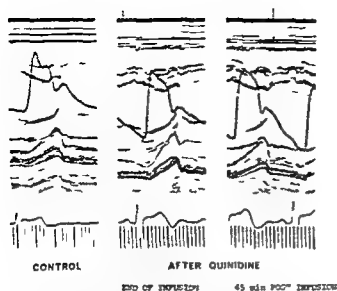


Fig 4 Echocardiogram and simultaneous carotid pulse tracing from a representative subject in the control state prior to the quinidine infusion (left) just at the end of the infusion (middle) and 45 minutes after the end of the infusion (right)

macokinetic values based on analysis of total and unbound quinidine concentrations for all subjects. The mean per cent of serum quinidine not bound to protein varied from 16.8 to 23.4%. Mean kinetic variables for total quinidine were: volume of distribution 20 liters/Kg, elimination half-life 6.3 hours, total clearance 3.8 ml/min/Kg. These values are very similar to those reported previously in a study of a different group of subjects. The elimination half-life of unbound quinidine (5.2 hours) was similar to that of total quinidine although the difference did reach statistical significance. However, the apparent volume of distribution of the unbound drug (8.8 liters/Kg) and the total clearance of unbound drug (19.8 ml/min/Kg) are more than four times greater than corresponding values based on total quinidine concentrations. The findings confirm those of a previous study<sup>1</sup> and clearly indicate that pharmacokinetic studies of quinidine based upon total rather than the pharmacologically active unbound fraction greatly underestimate the extent of distribution and the total metabolic clearance of the unbound drug. However, the half-life of elimination of total and unbound quinidine are similar inasmuch as the extent of protein binding appears to be essentially independent of total concentration.

Fig 5 shows representative serum concentration curves for total and unbound quinidine.

**Relation between pharmacokinetics and pharmacodynamics** Table II shows correlation coefficients for total and unbound serum quinidine concentrations measured at the end of the infusion and at 0.25-hour intervals thereafter versus pharmacodynamic changes at the corresponding times expressed as increases over the pre-infusion baseline values. Very few of the correlations approached statistical significance. Increases in heart rate were negatively correlated with total and unbound serum quinidine concentrations at all four points in time, indicating that higher quinidine concentrations were not associated with greater increases in heart rate. Similar negative associations were noted with changes in the corrected QT interval. No consistent association was observed between serum quinidine concentrations and QRS duration,  $V_1$ , or EF.

## Discussion

The effect of therapeutic doses of quinidine on the myocardial contractile state *in vivo* is incompletely understood. We therefore evaluated the effects of a single intravenous dose of quinidine on left ventricular performance in healthy individuals utilizing echocardiography as a sensitive and reliable noninvasive method for assessment of drug-induced changes in myocardial contractility.

The injection of a single therapeutic intravenous dose of quinidine significantly increased ventricular rate and prolonged the corrected QT interval. Effects lasted only for about 30 minutes after the end of the infusion, following which these variables reverted toward pre-quinidine baseline values. Quinidine-induced cardioacceleration observed in the present study was similar to that found in previous studies of intravenously administered quinidine lactate. The effect of quinidine on heart rate depends upon the specific experimental preparation. Reflex sympathetic stimulation may explain the acceleration of heart rate observed in intact conscious dogs given oral dihydroquinidine.<sup>1</sup> The quinidine-induced increase in heart rate was almost completely blocked by propranolol. In humans, however, 160 mg of oral propranolol daily did not prevent the increase in heart rate after an acute intravenous dose of quinidine seen without propranolol. In anesthetized open chest dogs, a reduction of the heart rate after intravenous quinidine was observed.<sup>11</sup> However, anesthesia and thoracoto-

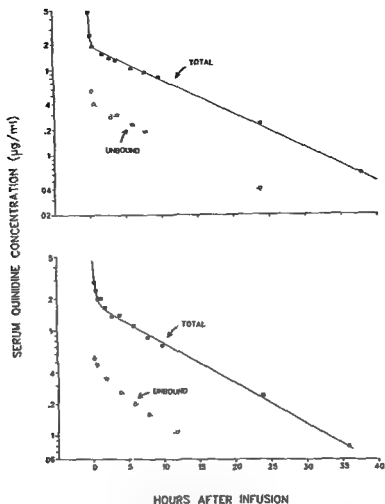


Fig 2 Serum concentrations of total and unbound quinidine in subjects W ■ (above) and D △ (below) following intravenous quinidine infusion. Also shown are pharmacokinetic functions determined by least squares regression analysis. See Table I for pharmacokinetic variables.

Table I Pharmacokinetics of total and unbound serum quinidine following a single intravenous dose

Subject	Age/Sex	Wt (Kg)	Mean ( $\pm$ SE) per cent unbound quinidine	Volume of distribution (liters/Kg)		Elimination half life (hours)		Total clearance (ml/min/Kg)	
				Total	Unbound	Total	Unbound	Total	Unbound
H O	33/M	70	19.7 ( $\pm$ 0.9)	2.5 <sup>a</sup>	11.94	6.66	6.03	4.3 <sup>a</sup>	22.88
W T	36/M	73	20.0 ( $\pm$ 0.9)	1.73	7.03	5.8 <sup>a</sup>	4.10	3.41	19.79
R b	34/F	52	27.4 ( $\pm$ 0.8)	1.65	7.25	4.7 <sup>a</sup>	4.13	4.01	20.20
D S	27/M	60	19.7 ( $\pm$ 0.4)	2.5 <sup>a</sup>	11.03	7.88	5.73	3.74	22.25
S M	27/M	70	18.7 ( $\pm$ 1.1)	1.53	6.40	4.99	3.54	3.55	30.89
P M	23/M	74	22.3 ( $\pm$ 0.6)	1.81	7.80	6.08	5.68	3.44	15.8 <sup>a</sup>
M H	22/F	52	20.9 ( $\pm$ 0.8)	2.27	9.49	6.24	5.21	4.19	21.05
R A	22/M	70	16.8 ( $\pm$ 0.3)	1.47	7.14	5.95	4.39	2.85	18.88
N B	23/M	64	23.4 ( $\pm$ 0.9)	3.00	11.6 <sup>a</sup>	6.66	6.19	5.21	21.79
W E	23/M	80	20.5 ( $\pm$ 0.5)	1.84	8.54	7.5 <sup>a</sup>	6.86	2.83	14.38
Mean ( $\pm$ SE)				2.03 ( $\pm$ 0.16)	8.83 ( $\pm$ 0.65)	6.26 ( $\pm$ 0.31)	5.18 ( $\pm$ 0.34)	3.76 ( $\pm$ 0.23)	19.80 ( $\pm$ 0.8 <sup>a</sup> )

Table II Relation of total and unbound serum quinidine concentrations to cardiac effects

Sampling time	Correlation coefficient of serum concentration versus				
	Increase in heart rate	Prolongation of QRS	Prolongation of QTc	Increase in V	Increase in EF <sup>a</sup>
<i>End of infusion</i>					
Total	-609 (p < 0.05)	-299	-393	-251	+ 007
Unbound	-605 (p < 0.05)	-305	-380	-308	-0.0
<i>0.25 hr post infusion</i>					
Total	-649 (p < 0.05)	+ 425	- 569 (p < 10)	+ 338	+ 534
Unbound	-742 (p < 0.02)	+ 255	- 662 (p < 0.05)	+ 411	+ 640 (p < 10)
<i>0.5 hr post infusion</i>					
Total	-616 (p < 0.03)	+ 010	- 506 (p < 10)	- 068	+ 151
Unbound	-437	- 145	- 337	- 222	- 0.9
<i>0.75 hr post infusion</i>					
Total	-512 (p < 1)	- 138	- 491 (p < 1)	+ 481	+ 417
Unbound	-596 (p < 1)	- 151	- 471 (p < 1)	+ 460	+ 514 (p < 10)

Level of significance given in parentheses when the correlation approached significance  
<sup>a</sup> Expressed as increments over pre quinidine baseline value

may as such can profoundly influence hemodynamics and myocardial contractility making it difficult to interpret the effects of quinidine in this setting.<sup>1</sup>

Quinidine produced no significant changes in systolic or diastolic blood pressure in our study. Ferrer and associates<sup>1</sup> observed a fall in aortic blood pressure after a single oral dose of 0.8 g of quinidine sulfate in only about 50% of healthy subjects. Quinidine induced hypotension seen under various experimental conditions has been attributed both to a central and peripheral effect of the drug but neither mechanism is well documented. The increase in heart rate and EF after intravenous quinidine in our study could represent reflex changes that offset any hypotensive effect of the drug. However James and Nadeau<sup>2</sup> observed a slight increase in heart rate in anesthetized dogs when quinidine was injected through the sinus node artery suggesting a direct stimulatory effect of quinidine on the sinus node. In any case a nontoxic intravenous dose of quinidine appears to have negligible hypotensive effects on resting healthy subjects. These findings do not necessarily apply to patients with impaired myocardial function.

Quinidine infusion caused a short acting but significant increase in V and EF. Like other indices of cardiac contractility these parameters are influenced by pre and afterload as well as by heart rate. Afterload as reflected by systolic and diastolic blood pressure did not increase and

therefore probably does not account for the positive inotropic effect of quinidine. Tachycardia however might have contributed to the improvement of contractility. In addition the anticholinergic action of quinidine by moderating the influence of the vagus on the heart might also have contributed to enhancing V and EF. In any case the findings indicate that a therapeutic dose of intravenous quinidine has no negative inotropic effects in healthy humans under the experimental conditions of this study.

The kinetic behavior of intravenous quinidine administered as the gluconate salt is similar to that of quinidine given as the lactate.<sup>3</sup> Protein binding of quinidine also was similar to that reported previously.<sup>1</sup> Use of total rather than unbound serum quinidine concentrations leads to considerable underestimation of the extent of drug distribution and metabolic clearance since only the unbound fraction in serum is available for distribution and clearance.

In contrast to a previous report<sup>1</sup> total and unbound quinidine concentrations failed to correlate with acute ECG changes. Edwards and colleagues demonstrated a weak correlation between quinidine plasma concentration and the QTc interval after a single oral dose. A stronger association between quinidine concentration and cardiac effects might arise if achievement of equilibrium between serum and tissues were assured as would occur during multiple-dose therapy.

## Summary

Ten healthy volunteers received 300 mg of quindine base as the gluconate salt by 15 minute intravenous infusion. Physiologic variables monitored before, during and for 24 hours after the infusion were electrocardiogram, systolic and diastolic blood pressure, echocardiogram, and carotid pulse tracing. During quindine infusion, mean ventricular rate increased by 18% (67.1 to 79.5 beats per minute) and corrected QT interval increased by 54% (0.44 to 0.68 sec). QRS duration did not change significantly, nor did systolic or diastolic blood pressure. Ejection fraction (EF) measured by echocardiography did not decrease during quindine infusion but rather increased by 12% (0.58 to 0.65). Mean rate of circumferential fiber shortening ( $V_f$ ) likewise increased by 22% from 1.15 to 1.40 per second. Over the 24 hours post infusion, all monitored physiologic variables fluctuated considerably, in the case of EF and  $V_f$ , apparently random variations over time were as great as those attributable to quindine infusion. Mean (and range) kinetic variables for quindine were: volume of distribution 2.03 (1.47 to 3.00) liter/Kg, elimination half life 6.3 (4.8 to 7.9) hours, total clearance 3.8 (2.8 to 5.2) ml/min/Kg. Neither total nor unbound serum quindine concentrations were significantly correlated with physiologic changes. Thus, intravenous quindine in the doses studied did not have negative inotropic effects in a series of healthy humans.

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### Limitations of the standard transthoracic electrocardiogram in detecting subendocardial ischemia

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In a recent study we showed that a left ventricular transmural ECG recorded from leads implanted on endocardial and epicardial muscle provided a reliable and instantaneous guide to the adequacy of subendocardial perfusion.<sup>1</sup> Under noninvasive clinical circumstances the presence of ischemia can be evaluated electrocardiographically only by use of the external transthoracic ECG where chest wall leads must be used.

The present study was designed to compare the relative sensitivities of the transthoracic and transmural ECGs to detect myocardial ischemia. We studied chronically instrumented dogs with patent coronary arteries. Global left ventricular ischemia was produced by giving isoproterenol (Isuprel Winthrop Laboratories New York N Y) and segmental ischemia was produced with graded degrees of coronary occlusion in dogs who were made to exercise. We measured regional myocardial blood flow while recording simultaneous transthoracic and transmural ECGs.

## Materials and methods

**Experimental procedure** Seven adult mongrel dogs weighing 21 to 26 kg were anesthetized with thiamylal sodium (Surralt) 30 mg/kg and placed

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on a Bird respirator anesthesia was maintained with methoxyflurane (Metofane). Catheters were placed into the descending aorta and left atrium as described previously.<sup>1</sup> Kongsberg pressure transducers (P 20) were placed in the descending aortic wall and Statham electromagnetic flow transducers and vascular occluders were placed around the circumflex coronary artery.

A hook electrode similar to that described by Guyton was inserted through the left ventricular wall and attached to the endocardium in an area perfused by the left circumflex coronary artery. A miniature electromyogram (EMG) electrode (Grass Instruments Inc) was attached to the epicardium which enabled us to record a left ventricular transmural ECG. All electrodes and catheters were tunneled subcutaneously to the back of the neck where they were externalized and protected by a jacket.<sup>2</sup>

**Measurements** The Konigsberg transducers were calibrated against the aortic catheters and pressure recorded on a Honeywell 1858 Viscometer. The pressure recordings were analyzed by planimetry to calculate myocardial oxygen demands from the tension time index (TTI) of Samoff and co workers and potential subendocardial blood supply from the diastolic pressure time index (DPTI). The ratio of these indices DPTI/TTI was used to assess the myocardial oxygen supply/demand balance as described previously.<sup>12</sup>

ECGs were recorded on a Viscorder using Sanborn ECG preamplifiers. To record the external transthoracic ECG areas on the dorsal, ventral and lateral aspects of the chest were shaved and standard plate electrodes attached to

**Table 1** Effect of isoproterenol and circumflex coronary artery occlusion on myocardial O<sub>2</sub> supply/demand indices

	Rest	Isoproterenol	Control exercise	Mod occlusion exercise	Severe occlusion exercise
HR (beats/min)	91.6 ± 6.1	206.1 ± 5.7	207.9 ± 10.7	216.4 ± 8.2	214.5 ± 7.0
DPTI (torr sec/min)	3.8 ± 1.37	18.1 ± 1.99	3.189 ± 2.57	3.104 ± 4.6	2.550 ± 1.61
TTI (torr sec/min)	1.513 ± 1.50	18.1 ± 1.58	3.510 ± 3.13	3.380 ± 3.05	3.302 ± 2.03
DPTI/TTI	2.60 ± 0.02	0.41 ± 0.04	0.92 ± 0.06	0.91 ± 0.09	0.78 ± 0.07

Values are mean ± SE

†  $p < 0.05$  vs. control exercise‡ Occlusion significantly different from control exercise ( $p < 0.05$ )

record directly across the chest in two directions. The internal transmural ECG was recorded directly across the left ventricular wall.

The total and regional coronary flows were measured by injecting batches (at least 3 million each) of 8–10  $\mu$  microspheres labeled with <sup>14</sup>C, <sup>3</sup>Sr, <sup>45</sup>Sc and <sup>125</sup>I into the left atrium. Arterial reference samples were withdrawn continually (15 ml/minute) for 120 seconds at rest and 90 seconds during exercise or isoproterenol infusion as described previously.<sup>5</sup>

After completing the chronic experiments the dogs were anesthetized with Surltal and killed by an intracardiac injection of potassium chloride. Hearts were removed and placed in ice cold saline solution for 24 hours to facilitate subsequent sectioning. The anterior and posterior left ventricular walls were cut into inner middle and outer myocardial layers of approximately equal thickness and analyzed for radioactivity in a Nuclear of Chicago pulse height analyzer. Total and regional flows were calculated as described previously.

#### Test procedures

**Isoproterenol** Isoproterenol, a drug known to cause global subendocardial ischemia,<sup>6</sup> was infused into seven dogs at doses ranging from 2.5 to 5  $\mu$ g/kg/minute. Radioactive microspheres were injected before and after these infusions were given.

**Exercise** Dogs were selected for the exercise series by ensuring that they would run on a treadmill before subjecting them to thoracotomy and chronic instrumentation. The exercise studies were carried out 14 to 21 days after recovery from thoracotomy at a time when there was no clinical evidence of anemia, fever or other sign of illness.

The initiation of exercise testing consisted of

running dogs on a treadmill at a work load and grade sufficient to produce a near maximum heart rate response. During this steady state level of near maximum treadmill testing we recorded transmural and transthoracic ECGs, mean and phasic coronary blood flow and intravascular pressures.

Following this initial near maximum exercise test (usually on a different day) we ran dogs at work loads sufficient to raise heart rate to approximately 200 beats/minute. We produced moderate coronary constriction during this steady state level of exercise by narrowing the circumflex coronary artery until mean coronary flow was reduced by approximately 30%. We produced severe coronary constriction by narrowing the circumflex coronary artery further to reduce mean coronary blood flow during steady state exercise to approximately 55% below the level achieved during comparable work loads without coronary narrowing. Each dog underwent at least one treadmill test where only moderate or severe coronary constriction was imposed. Regional and phasic flow measurements and intravascular pressures were made when the coronary artery was either left open, narrowed moderately or narrowed severely.

Statistical analysis consisted either of *t* test or analysis of variance and the Scheffe test ( $p \leq 0.05$  was used for statistical significance).

#### Results

**Isoproterenol** Isoproterenol caused varying degrees of tachycardia and diastolic hypotension in all dogs and consequently produced a marked fall in the supply/demand ratio (DPTI/TTI) (Table 1). Ischemic changes developed on transmural electrocardiogram in each of with unobstructed coronary artery.

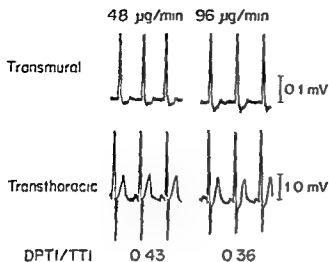


Fig 1 ECG responses to isoproterenol infusion

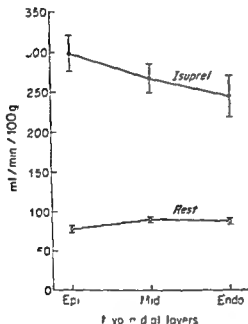


Fig 2 Effect of isoproterenol on left ventricular flow distribution.

DPTI/TTI was reduced below 0.5 by isoproterenol infusion (Fig 1). In contrast only slight J point depression or no ECG changes occurred during simultaneous recording of the transthoracic ECG in these dogs.

The dosage required to produce the ischemic ECG changes varied in different dogs: two developed ischemia at the lowest dose and three required higher doses. DPTI/TTI was highest (0.92 and 1.01) in two dogs that did not develop ischemia despite a 5 µg/kg/minute isoproterenol infusion.

During the test period coronary blood flow was

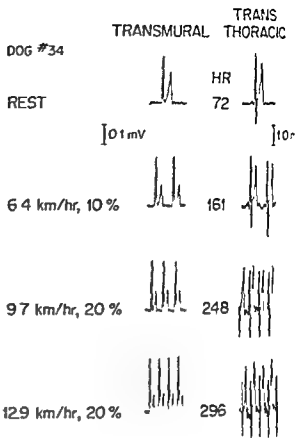


Fig 3 Transmural and transthoracic ECG responses during near maximum exercise test.

distributed preferentially toward the subendocardium: endocardial/epicardial flow was 1.13 (Fig 2 Table II). Although left ventricular blood flow increased to all myocardial layers during the isoproterenol infusion which produced ischemia in the five dogs, this flow became redistributed away from subendocardial muscle. Subepicardial flow rose 288% while subendocardial flow rose by only 180%. Consequently the endocardial/epicardial flow fell from 1.13 to 0.81 ( $p < 0.05$ ). Flow distribution remained homogeneous (epicardial/endocardial flows were 0.98 and 1.03) during the isoproterenol infusion in the two dogs which did not show ischemia on the transmural ECG.

**Exercise.** No ischemic changes developed on either the transmural or transthoracic ECG during the initial near maximum treadmill test (heart rate  $267 \pm 9$  beats/minute) in seven dogs. Despite the severe tachycardia, the transmural ECG recordings showed a stable baseline and the recording fidelity was such that each record could be analyzed readily (Fig 3). In contrast, two of seven standard external transthoracic ECGs

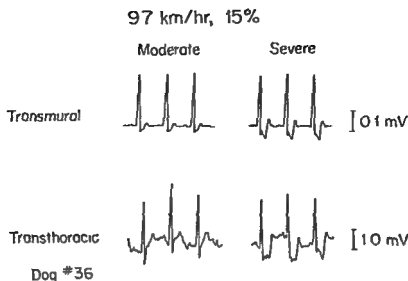


Fig 4 Transmural and transthoracic ECG responses to moderate and severe coronary occlusion

Table II Effect of isoproterenol and circumflex coronary artery occlusion on left ventricular blood flow

	Rest	Isoproterenol	Control exercise		Mod occlusion exercise		Severe occlusion exercise	
			LAD area	Circumflex area	LAD area	Circumflex area	LAD area	Circumflex area
Mean flow (ml/100 gm min)	84.7 ± 4.8	96.9 ± 6.3	271.7 ± 28.0	278.6 ± 42.0	308.5 ± 33.9	198.9 ± 17.1	316.3 ± 33.5	168 ± 17.8
Endo/epi flow	1.13	0.81	0.99	1.05	1.06	0.43	0.98	0.45*

Values are means ± SE

Isoproterenol significantly different from rest ( $p < 0.05$ )

\*Occlusion significantly different from control exercise ( $p < 0.05$ )

could not be interpreted during maximum treadmill testing because of motion artifact

During treadmill testing moderate coronary narrowing (29% reduction in exercise flow) produced ischemia which was evident in the transmural ECG in each of the seven dogs. The simultaneously recorded standard external electrocardiogram however showed either no change or only slight J point depression at this time. It was only with severe coronary narrowing (sufficient to reduce exercising coronary flow to 55% below control levels) that we could produce ST depression on the external transthoracic ECG (Fig 4). Such narrowing caused alarming changes in the transmural ECG and resulted in ventricular fibrillation in one dog (Fig 5).

Transmural and regional flow to the anterior myocardium supplied by the unobstructed left anterior descending coronary artery remained

relatively constant ( $271 \pm 27$   $309 \pm 34$  and  $316 \pm 34$  ml/100 gm minute) during the steady state level of activity while the circumflex coronary artery was opened or moderately or severely narrowed.

Moderate narrowing of the circumflex coronary artery decreased mean transmural flow in the area supplied by that artery from  $287 \pm 42.0$  to  $198.9 \pm 17.1$  ml/100 gm minute. Epicardial muscle flow was however maintained at prestenotic levels while flow to the midmyocardial and subendocardial muscle layers was reduced significantly (Fig 6 Table II). Subepicardial muscle blood flow could not however be maintained when the circumflex coronary artery was narrowed severely enough to reduce mean coronary flow to  $126.8 \pm 17.8$  ml/100 gm minute (55% below control values) subepicardial flow fell from  $261.1 \pm 38.2$  to  $166.5 \pm 25.6$  ml/100

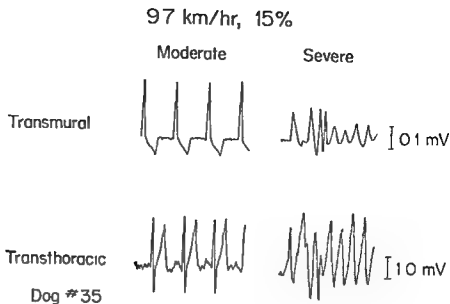
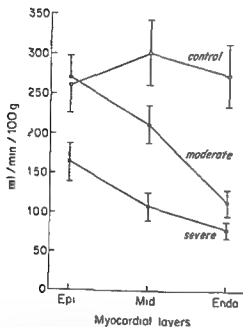


Fig 5 Transmural and transthoracic ECG responses to moderate and severe coronary occlusion



6 Coronary blood flow response to moderate and severe occlusion during exercise

minute while subendocardial flow was reduced further to  $79.7 \pm 11.8$  ml/100 gm min (Fig 6)

#### Discussion

The extreme vulnerability of left ventricular endocardial muscle to ischemia is emphasized by reports showing that most myocardial infarctions in patients with coronary artery disease are limited to or most severe in the left ventric

ular inner shell. Recent studies in dogs with graded coronary stenoses show that moderate coronary narrowing restricts subendocardial flow preferentially with subepicardial flow remaining normal. Subendocardial underperfusion was always most severe with coronary narrowing that reduced flow transmurally.<sup>11</sup> Our data are consistent with the above findings and show that the standard transthoracic ECG recorded from chest wall leads is relatively insensitive to moderate subendocardial underperfusion; transmural hypoperfusion is necessary in order to be detected by the monitoring technique which is used most often in clinical practice.

We used isoproterenol, a drug known to produce subendocardial ischemia and necrosis,<sup>12</sup> to test the transmural lead system since our previous studies have demonstrated that with isoproterenol coronary flow is redistributed away from the subendocardial muscle. Although isoproterenol caused a marked augmentation in total left ventricular flow ( $847 \pm 48$  to  $269.8 \pm 26.3$  ml/100 gm minute), subepicardial flow rose by 288% while subendocardial flow rose by only 180% resulting in an endocardial/epicardial flow of 0.81. Ischemia became evident on the transmural ECG but the simultaneously recorded transthoracic ECG remained normal. As with our previous reports, the supply/demand ratio (DPTI/TTI) was useful in predicting the ischemia produced by isoproterenol.<sup>13</sup> Prominent ST depression was seen in the transmural ECG in

each of five dogs when this ratio was  $< 0.5$  and did not develop in two other dogs (receiving comparable isoproterenol infusions) with  $DPTI/TTI > 0.50$ . This ratio however is useful only when the coronary arteries are unobstructed since the diastolic blood pressure is always reduced beyond any flow limiting coronary stenosis especially when coronary blood flow is increased as with exercise.<sup>13,14</sup> Consequently ischemia would be expected to develop at a much higher  $DPTI/TTI$  when coronary stenosis is present.

It is not surprising therefore that ischemia became evident on the transmural ECG during treadmill testing in all dogs with coronary stenosis even though  $DPTI/TTI$  was always  $> 0.50$  ( $0.91 \pm 0.09$  with moderate stenosis and  $0.78 \pm 0.07$  with severe stenosis). As with the ischemia produced by isoproterenol the transthoracic ECG remained normal during exercise with moderate coronary stenosis and preferential subendocardial underperfusion and changed only when we made the stenosis more severe and caused transmural hypoperfusion. The most pronounced redistribution of coronary blood flow away from the subendocardium (endocardial/epicardial flow falling from 1.05 to 0.43) occurred with coronary narrowing sufficient to reduce exercising coronary blood flow only 29% below levels achieved during exercise with patent coronary arteries. This marked redistribution of flow occurred because subepicardial vessels were able to dilate sufficiently to maintain coronary blood flow at prestenotic levels while endocardial flow fell 57%.

Since the early work of Hellerstein and Katz and Wolferth and co workers,<sup>15</sup> ST depression has been the hallmark of ischemia which is presumed to be limited to the subendocardial region. Our studies provide evidence that while the subendocardial muscle is indeed ischemic when the transthoracic ECG shows ST changes this ischemia is transmural rather than confined to the inner shell. Our combined use of the transmural ECG and direct blood flow measurements (microspheres) show that the transthoracic ECG is of limited value in detecting early subendocardial relative underperfusion.

Biochemical support of our conclusions about the limitations of transthoracic ECGs can be marshalled from the studies of Case and co workers<sup>16</sup> and Scheuer and Brachfeld<sup>17</sup> who

reported coronary sinus lactate and potassium increases during graded coronary occlusion that precede the ischemic ST segment changes seen on the external transthoracic ECG. The need to be suspicious of the limitations of noninvasive clinically available techniques in detecting subendocardial ischemia has been emphasized by others.<sup>18</sup> Studies by Sayen and associates<sup>19</sup> showed that even myocardial surface electrocardiography had limited sensitivity in detecting subendocardial ischemia. They observed marked ST segment changes on an intramural ECG with severe reductions of subendocardial tissue  $P_{O_2}$  and contractility before epicardial leads detected the ischemia.

We realize that a multiple chest lead system may be 10% to 20% more sensitive in detecting ischemia than one or two transthoracic lead systems which are often used clinically and which we used in our dogs.<sup>20</sup> We realize also that exercise electrocardiography is less sensitive for single than double or triple vessel disease. However we do not feel that these factors can explain the lack of our ability to use the standard transthoracic ECG to detect ischemia which is limited to the subendocardium. Isoproterenol produced global subendocardial ischemia<sup>14</sup> while the transthoracic ECG did not change appreciably.

The results of our study have potential clinical implications in that our documentation of limitation of the transthoracic external ECG clarifies why some patients who complain of angina during treadmill testing do not show ischemic ECGs when chest leads are monitored. The occurrence of subendocardial ischemia before ST depression is seen on the external ECG together with the need for transmural ischemia to be present before this lead system is sensitive suggests that extreme caution must be practiced when patients are made to exercise for prolonged periods at work loads which elicit signs of ST depression on the external ECG.

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# Sialic acid-depleted red cells following acute myocardial infarction

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Sialic acid (SA) is the terminal moiety of a membrane glycoprotein and is responsible for the negative surface charge on the red blood cell (RBC). Chien and others have reported decreased red cell SA in a patient with a stroke while Resnitzky and others<sup>1</sup> have demonstrated a reduction in red cell electrophoretic mobility (EM), a measure of surface charge in patients with acute myocardial infarction and venous thrombosis of the lower extremities. Because these observations suggest that a relationship between chemical changes on the red cell and disturbances of intravascular hemostasis may exist, erythrocyte SA in patients following acute myocardial infarction was measured and the hemodynamic effects of SA depleted red cells in an animal model were studied.

## Materials and methods

**Patients** Within 48 hours of hospital admission blood samples were collected in heparinized tubes by venipuncture from patients with acute myocardial infarction.

Following centrifugation of 4 ml of collected human blood at 3 800 rpm for 18 to 20 minutes at room temperature the plasma and buffy coat

were discarded. The red cells were washed three times in 0.9% saline solution and 9 volumes of fresh 0.9% saline solution was added to make a 1:10 erythrocyte saline suspension. SA was extracted from the washed erythrocyte suspension by adding 3 ml 0.4N H<sub>2</sub>SO<sub>4</sub> to the erythrocyte suspension placed in a water bath at 80° C for 1 hour. To each tube 0.6 ml 15% K<sub>2</sub>Fe(CN)<sub>6</sub> followed by 0.6 ml 30% Zn(CH<sub>3</sub>COO)<sub>2</sub> were added. This was then centrifuged at 2 400 rpm for 5 minutes. The clear supernatant was removed and the SA content was measured by the thiobarbituric acid assay described by Warren<sup>2</sup> and expressed in micromoles per 0.1 ml RBCs.

SA reference values were obtained from a control group of healthy men and women 22 to 45 years of age. The diagnosis of myocardial infarction was established by clinical impression, electrocardiograms and enzyme determinations.

**Animals** Seven mongrel dogs (10 to 12 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg), intubated and placed on a volume respirator delivering room air and mean femoral artery pressure. Heart rates were continuously monitored on an oscilloscope and intermittently recorded. The pulmonary microcirculation was filmed according to the technique described by Wax.<sup>3</sup> The widths of typical alveolar capillary beds were measured in microns and changes were expressed as a percentage of control values. After obtaining control hemodynamic measurements and blood samples for control determinations of red cell SA and EM, five

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**Table 1** Dog red cell SA and EM after neuraminidase and storage

	SA ( $\mu\text{mol}/0.1$ ml RBC)	EM ( $\mu\text{sec}/\text{volt}/$ cm at 25°C)
Reference value	$0.043 \pm 0.002$ (SEM)	$1.98 \pm 0.07$
Neuraminidase	$0.028 \pm 0.003$ ( $p < 0.001$ )	$1.5 \pm 0.08$ ( $p < 0.001$ )
Reference value	$0.043 \pm 0.002$	$2.02 \pm 0.01$
Stored blood (in vitro)	$0.024 \pm 0.003$ ( $p < 0.001$ )	$1.87 \pm 0.02$ ( $p < 0.001$ )

SEM = standard error of mean

animals were given intravenous *Vibrio cholerae* neuraminidase (VCN),\* 875 units/kg, free of proteolytic activity and lecithinase at pH 5 while two animals were given the same dosage of boiled VCN. Serial measurements of red cell SA and EM were made and films of alveolar capillary blood flow were taken every half hour. Mean femoral artery pressures and heart rates were intermittently recorded.

Six other dogs were prepared like the first group and, in addition, a Carolina flow probe was put around the pulmonary artery and a Swan Ganz catheter positioned in the right heart outflow tract so that measurements could be made of cardiac output, pulmonary artery, and pulmonary capillary wedge pressures. This group was given VCN intravenously (875 units/kg) and subsequent changes in red cell SA and EM were measured and hemodynamic variations recorded.

From each of nine splenectomized dogs 500 ml of whole blood was drawn under sterile conditions and stored in acid citrate dextrose (ACD) solution at 4°C for 28 days and 3 units for 48 hours. Three dogs were autotransfused through in-line filters with 28 day old blood and films of the pulmonary microcirculation were taken intermittently. Three other dogs were given 28 day old blood with hemodynamic measurements recorded and three dogs were autotransfused with 48 hour old blood as a control.

The determination of EM is based upon the relationship between the rate of movement of a particle in an electric field and the magnitude of its surface potential as described by Helmholtz

and Smoluchowski.<sup>7</sup> Dog blood collected in heparinized tubes from a Silastic catheter in the femoral vein was centrifuged at 2400 rpm (buffy coat and plasma discarded and the red cells washed three times in 0.9% saline solution and suspended in a sorbitol solution with an adjusted pH of 7.4 (sodium bicarbonate buffer) and an ionic strength of 0.01. The sorbitol erythrocyte suspension was placed in the cell of the Zeta meter\* where EM was determined and expressed in microns per second per volt per centimeter corrected for temperature at 25°C.

The statistical analysis of data was done on a Hewlett Packard calculator 9810A programmed for the paired t test.

## Results

The mean erythrocyte SA value in 26 patients following acute myocardial infarction was  $0.021 \pm 0.001$  (SEM)  $\mu\text{mol}/0.1$  ml RBCs compared with a reference value of  $0.043 \pm 0.002$  ( $p < 0.01$ ).

In five dogs mean erythrocyte SA decreased from  $0.043 \pm 0.002$  to  $0.028 \pm 0.003$  ( $p < 0.001$ ) and mean EM decreased from  $1.98 \pm 0.07 \mu\text{sec}/\text{volt}/\text{cm}$  at 25°C to  $1.5 \pm 0.08$  ( $p < 0.001$ ) after neuraminidase. Mean cardiac index decreased from  $2.3 \pm 0.22$  to  $1.3 \pm 0.16$  ( $p < 0.001$ ) and the mean width of typical alveolar capillary beds decreased  $42.6\% \pm 0.5\%$  ( $p < 0.01$ ). In three dogs following autotransfusion of 500 ml of 28 day old blood with a mean erythrocyte SA of  $0.024 \pm 0.003$  and mean EM of  $1.87 \pm 0.02$ , the mean cardiac index decreased from  $2.0 \pm 0.21$  to  $1.5 \pm 0.21$  ( $p < 0.2$ ) and the mean width of alveolar capillary beds decreased by  $21.7\% \pm 0.9\%$  ( $p < 0.01$ ).

No significant changes in SA, EM, cardiac index, or alveolar capillary beds were seen following injection of boiled neuraminidase.

## Discussion

In the patients studied with acute myocardial infarction red cell SA was reduced by about one third while in the dog a one third or more reduction of red cell SA produced by the intravenous injection of neuraminidase and autotransfusion of 28 day old blood resulted in myocardial depression and decreased alveolar capillary blood flow (Tables I and II). By causing perfuse

Table II Hemodynamics after neuraminidase and stored blood

	Cardiac index (L/min/m <sup>2</sup> )	Mean femoral artery pressure mm. Hg	Mean heart rate (beats/min)	Mean pulmonary artery pressure (mm Hg)	Mean pulmonary capillary wedge pressure (mm Hg)
Control	2.3 ± 0.2 (SEM)	111	129	15	—
Neuraminidase	1.3 ± 0.16 (p < 0.01)	70	118	11	—
Control	2.0 ± 0.21	133	133	15	3.7
Stored blood (4 weeks)	1.5 ± 0.21 (p < 0.2)	130	130	20	5.5
Control	2.0 ± 0.21	133	153	—	—
Fresh blood	3.2 ± 0.31 (p < 0.1)	150	184	—	—

SEM = standard error of mean.

defects in the heart and lungs red cell clumping (created by a reduction of repulsive electrostatic forces and clearly seen in the films of the pulmonary microcirculation) may be the mechanism responsible for these hemodynamic changes.

Although the percentage reduction in cardiac index and pulmonary flow patterns was similar the hemodynamic changes following neuraminidase were greater than those following stored blood (Table II). This difference is due to a greater concentration of SA depleted red cells produced by neuraminidase which caused no effects when boiled and injected intravenously.

While the decrease in SA after neuraminidase and storage was in a similar range (35% and 44% respectively) the decrease in electrophoretic mobility after neuraminidase was 24% compared with 7% after storage (Table I). However the addition of calcium chloride to the stored blood before EM determinations all but eliminated this difference suggesting that citrate may increase the negative charge on the red cell by binding cations.

The stability of the glycosidic linkage between SA and the rest of the glycoprotein makes enzymatic disruption a likely mechanism for the reduction of red cell SA following acute myocardial infarction although the source of the enzyme is unknown.

If the same relationship between red cell SA senescence and the reticuloendothelial system described by Landaw<sup>8</sup> in the mouse exists in the human then the effects of SA depleted red cells should last about as long as it takes to clear them from the general circulation.

### Summary

A reduction of red cell SA in patients following acute myocardial infarction is reported and the effects of SA depleted red cells on cardiac index and alveolar capillary blood flow in the dog are described. The mean red cell SA in 26 patients following acute myocardial infarction was  $0.021 \pm 0.001$  compared with a mean of  $0.031 \pm 0.002$   $\mu\text{mol}/0.1$  ml RBC in 12 normal subjects ( $p < 0.01$ ).

In five dogs injected with neuraminidase an enzyme which removes SA from the red cell membrane a 43% decrease in mean cardiac index from  $2.3 \pm 0.22$  to  $1.3 \pm 0.16$  ( $p < 0.01$ ) occurred. In films of the pulmonary microcirculation the mean widths of typical alveolar capillary beds decreased  $42.6\% \pm 5\%$  ( $p < 0.01$ ). In three other dogs, autotransfusion with SA-depleted stored blood resulted in a 20% decrease in mean cardiac index from  $2.0 \pm 0.21$  to  $1.5 \pm 0.21$  ( $p < 0.2$ ) and a  $21.7\% \pm 0.9\%$  ( $p < 0.01$ ) decrease in mean widths of typical alveolar capillary beds. We conclude that a reduction of red cell SA follows acute myocardial infarction and that SA depleted red cells decrease cardiac index and alveolar capillary blood flow in the dog.

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# The abnormal heart rate response to a deep breath in borderline labile hypertension: a sign of autonomic nervous system dysfunction

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Patients in this gray zone area of essential hypertension with somewhat elevated casual blood pressure levels on one visit but normal on another constitute a very common disorder in this country comprising about 10% of adults but perhaps twice that prevalence among university age students. In describing patients in this marginal pressure zone some prefer the term 'labile hypertension' which assumes that some pressures are occasionally normal and hypertension target organ damage is absent.<sup>1,2</sup> Others prefer the term 'borderline hypertension' appropriately noting that a few readings with a span of only several mm Hg on either side of some critical point e.g. 140/90 mm Hg is a highly artificial and certainly objectionable way to define a distinct nosologic 'labile' category.<sup>3</sup> This present study escapes that criticism however because the patients reported here demonstrated a marked pressure span, one easily accepted as 'labile' but too excessive to be considered merely 'borderline'. They are therefore henceforth referred to in this study as having 'labile hypertension' (LHT).

The problem at once confronting the clinician is how seriously to view these occasional blood pressure elevations as most such persons do not become hypertensive patients: only 12% of young men with labile readings advanced to sustained hypertension over a 20 year interval slightly

higher as well as somewhat lower rates have been noted also over other similar extended periods.<sup>4,5</sup> However the vast majority of such persons commonly younger people are not destined to become permanent hypertensives and the early institution of chronic perhaps even life long drug therapy would appear a therapeutic adventure of dubious value and entailing certain drug risks. Perhaps such youngsters are best considered as normal persons with an orienting or defense reflex somewhat more lively than most.<sup>6,7</sup>

That such transient elevations cannot be cavalierly disregarded however is dramatically shown by their increased incidence of vascular complications, an overall reduction in life expectancy and the occasional development of sustained hypertension.<sup>8</sup> Over a 50 month period for example a slowly changing hemodynamic pattern has been observed in a minority of LHT patients to one of lower cardiac output, lower heart rate and increased peripheral resistance, the standard pattern of sustained essential hypertension.<sup>9</sup> While such a course can occur, the problem is selection of that unfortunate minority from the preponderant majority of healthy but similarly labile normal individuals not so destined to later become ill hypertensive patients. A current capability of such a clinical distinction is not available and further research on the earlier phases of hypertension is sorely needed.

A distinct deficit of autonomic neural control of the heart in labile or borderline hypertension was demonstrated in 1971 by Julius Pascual and London<sup>10</sup> who clearly showed in these patients a subnormal rise in the heart rate with full nitroprusside following complete beta adrenergic blockade. Their important conclusion that

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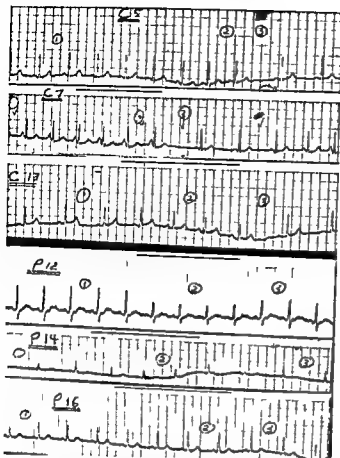


Fig 1 Three illustrative controls (C) above and three labile hypertensive patients (I) below. The numbers with C and I refer to the subject designation in Table II. The circled numbers 1, 2 and 3 refer to heart rate intervals at rest inspiration and expiration. The horizontal bar above each strip marks the deep inspiration.

onstrated a deficit of parasympathetic inhibition is supported by the work reported here. Whether such a deficit is predictive of subsequent sustained hypertensive disease can be established only by long term prospective study.

#### Methods

All patients meeting the prescribed blood pressure criteria were recruited consecutively and prospectively from the Hypertension Clinic of Grant Hospital and from the consulting practice of the author. Their clinical characteristics are depicted in Table I. To be eligible the blood pressure had to be less than 150/100 mm Hg supine at the time of the inhalation test and after a short period of supine rest (5 to 10 minutes); all but two had systolic pressures of 133 mm Hg or less and all but four had diastolic pressures of 80 mm Hg or less. Also at any visit during the preceding 30 months two resting blood pressure

Table I Clinical characteristics of subjects

	Controls	Patients
Male/Female	13/3	5/11
Age (years)	40 $\pm$ 1 <sup>a</sup>	41 $\pm$ 1 <sup>a</sup>
Height (cm)	170 $\pm$ 6	169 $\pm$ 4
Weight (kg)	77 $\pm$ 10	71 $\pm$ 10
Blood pressure (mm Hg)		
At time of test		
Systolic	117 $\pm$ 8	131 $\pm$ 6
Diastolic	73 $\pm$ 4	80 $\pm$ 9
Maximum in 30 months		
Systolic	—	171 $\pm$ 11
Diastolic	—	100 $\pm$ 9

<sup>a</sup>  $\pm$  1 standard deviation

values while or while not on therapy had to be greater than 150/100 mm Hg and the systolic pressure had to be at least 25 mm Hg greater than at the time of the inhalation test. The span of one patient was less: 148/80 mm Hg on the test day and a maximum earlier value of 160/100 mm Hg. Eight patients exhibited systolic rises on other visits of at least 10 mm Hg greater than on the test day reaching levels of 180/90 mm Hg or greater. Two alcoholics and two distance runners had to be excluded (see below). All patients were ambulatory active and felt well. None had or had ever had, proteinuria, azotemia, hemorrhage, or exudative retinopathy, roentgenographic cardiomegaly, ventricular hypertrophy by electrocardiography, congestive heart failure, or vascular ischemic disease of heart or brain. All were clinically diagnosed as having borderline labile essential hypertension and none had received drug therapy or contraceptive steroids for at least one month preceding the test.

The normal controls were similarly consecutively recruited from a group of healthy subjects undergoing routine outpatient periodic physical examination. All exhibited resting supine pressures of 140/100 mm Hg or less; all but two had pressures of 120/70 mm Hg or less. The only exclusions were four alcoholics and two distance runners. This exclusion was necessitated by the fixed heart rate response of the alcoholics to the inhalation test maneuver and the exaggerated response of the runners. These individuals are currently under separate study.

The body weight of the two groups was comparable. While the average weight and height of the control group were slightly more than those of the patient group, 77 kilograms and 1.70 cm

Table II Pulse rate response from rest to maximal inspiration and expiration (beats/minute b/m and percent change % Δ)

	Normal controls						Labile hypertension patients					
	1 Rest b/m	2 Inspiration b/m % Δ		3 Expiration b/m % Δ			4 Rest b/m	5 Inspiration b/m % Δ		6 Expiration b/m % Δ		
		a	b†	a	b†	c†		a	b†	a	b†	c†
1	66	86	30	57	14	34	81	84	4	81	0	4
2	68	81	19	55	19	32	94	97	3	94	0	3
3	63	70	11	56	11	20	57	64	12	54	5	16
4	59	77	31	43	27	44	94	100	6	100	-6	0
5	86	97	13	59	31	38	86	91	6	75	13	18
6	61	75	23	50	9	27	103	111	8	100	3	10
7	91	97	6	57	37	41	81	86	6	75	7	13
8	63	77	22	57	10	26	64	73	14	61	5	10
9	68	81	19	63	7	22	86	86	0	75	13	13
10	51	60	18	50	2	17	77	84	9	73	5	13
11	50	84	29	47	28	44	75	88	17	70	7	20
12	64	68	26	46	15	30	94	97	3	94	0	3
13	65	81	25	56	14	31	79	88	11	73	0	17
14	58	75	29	50	14	33	64	81	38	63	2	20
15	81	97	20	70	14	28	86	94	0	84	-2	6
16	51	70	37	48	6	31	84	84	0	81	4	4
Means	66	80	22	54	17	31	82	88	8	79	4	11
Significance of difference from normal controls*												
Significance of differences from previous state 1 to 2a 1 to 3a 2a to 3a 4 to 5a and 4 to 6a not significant 5a to 6a												

$$\begin{aligned}
 & * p < 0.05 \quad = < 0.005 \quad = < 0.0005 \\
 & \dagger b = \frac{2a-1}{1} \times 100 \quad 3b = \frac{1-a}{1} \times 100 \quad 3c = \frac{2a-3a}{2a} \times 100 \quad 5b = \frac{5-4}{4} \times 100 \quad 6b = \frac{4-6a}{4} \times 100 \quad 6c = \frac{5a-6}{5a} \times 100
 \end{aligned}$$

versus 71 kilograms and 165 cm only three controls and three patients exceeded an ideal weight range by more than 10 kilograms. A single subject was underweight, a patient weighing 52 kilograms and 170 cm tall. The slight age discrepancy between patients and controls is considered below (see Discussion).

All controls but one were Caucasian, as were all patients but one.

While still supine and after the blood pressure had been recorded, subjects were simply asked to inhale as deeply as possible but without gasping and then to comfortably exhale without pausing to a resting position while the heart rate was monitored by electrocardiography with a standard paper speed of 25 mm per second and a horizontal marker delineating by gross observation of the subject the visible inspiratory effort (see Fig. 1). Intervals were measured from the peaks of the R waves. The test was performed

three times at approximately 30 second intervals and the complex with the longest expiratory pause (slowest expiratory heart rate) was used for statistical analysis of the control inspiratory and expiratory intervals. The inspiratory interval selected was the shortest one during inspiration. The expiratory interval used was the longest of the three intervals immediately following termination of the deep inspiration. The control interval used was the average by visual inspection of the four intervals immediately preceding the inspiratory effort. Performance of this maneuver in the standing position did not increase test sensitivity, i.e., expiratory slowing of pulse rate was less not more in the standing position. The deep breath maneuver in normal supine subjects greatly exaggerated the heart rate response over that noted during mere resting ventilation from one of a magnitude scarcely detectable on gross ECG inspection to those conspicuous mean responses of +22% inspiration and -17% expiration listed in Table II. Resting ventilation heart

\* 1st and 2nd Blood Pressure Study, Metropolitan Life Insurance Co. Society, February, 1959.

Pulse Rate Change (%) from Rest (R) with Inspiration (I) and Expiration (E) in Controls (C) and Patients (P)

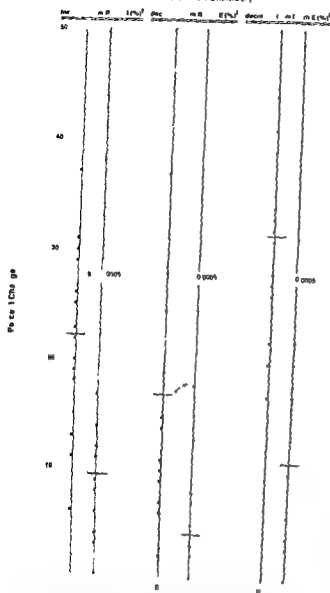


Fig 2 A comparison of percent change of pulse rate response (I) of normal controls (C) and patients with labile hypertension (P) to a deep inspiration (I) compared to rest (R) left pair to expiration (E) compared to rest middle pair to expiration compared to inspiration right pair. For method of calculation of these ratios see legend to Table II

rate responsiveness in these normal subjects was limited to approximately 4% as has been well established. LHT patients showed minimal responsiveness to either normal resting ventilation or a deep breath.

The significance of differences between mean values within each group and also between controls and patients was assessed respectively by paired and unpaired Student's *t* test.

## Results

The very highly significant differences in heart rate response between normals and LHT to a deep breath are shown in Fig 2. These differences and also the change within each group 'normal' or LHT' resulting from moving from rest to inspiration to expiration are stated in Table II. Several illustrative examples are shown in Fig 1.

The resting supine heart rate in LHT was elevated 82 vs 66 beats/min ( $P < 0.0005$ ). All but 3 patients had resting rates of 75 beats/min or greater; those 3 also maintained lower than average rates with both inspiration and expiration. All but 3 controls had resting rates below 75 beats/min; those 3 maintained higher than average rates with both inspiration and expiration.

On statistically contrasting the two groups, LHT patients achieved a higher mean rate with inspiration than normals: 88 versus 80 beats/minute ( $P < 0.025$ ), but because they started from a higher baseline their higher absolute rate reflected a very highly significantly lower percentage increase in heart rate than normals: 9 versus 22% ( $P < 0.0005$ ). The highest percentage increases in both normals and LHT occurred in those individuals with lower than average resting rates. With expiration the LHT group decreased their mean rate only 4% from its resting value, whereas normals decreased theirs by 17%, a highly significant contrast ( $P < 0.0005$ ). Only two of the LHT group decreased their rate by more than 8%; all but three of the normals decreased their rate by more than 8% and all but five by more than any patient.

On statistically studying alterations of heart rate within each group separately, significant changes are largely limited to the normal controls. They very significantly ( $P < 0.005$ ) increased their heart rate with inspiration from 66 to 80 beats/minute and then decreased it to 60 beats/minute with expiration, a significant decrease as compared to their resting rate ( $P < 0.0025$ ) and a very significant decrease compared to their peak inspiratory heart rate ( $P < 0.0005$ ). Patients did not so decrease their rate; their change with inspiration was not significant ( $P > 0.05$ ) and their change with expiration was also not significant when compared to their resting rate and was only barely so ( $P < 0.05$ ) when compared to their peak inspiratory rate.

## Discussion

This study describes a particular physiologic characteristic of a group of patients with marginal or borderline blood pressure levels associated with unmistakable lability. When compared to normals the lack of heart rate response to a deep breath in LHT was distinctive. While LHT patients at rest started with a more rapid pulse 82 beats/minute vs 66 beats/minute for normals ( $P < 0.0005$ ) their pulse rate neither increased significantly with inspiration nor decreased with expiration as compared to its resting level ( $P > 0.05$  (see Table II). Normal subjects on the other hand, very significantly ( $P < 0.0005$ ) increased their heart rate 22% on inspiration and decreased it 17% on expiration ( $P < 0.0025$ ) as compared to its resting value. Their rate at peak inspiration only equalled the mean resting rate of LHT patients who maintained a more rapid but unchanging rate throughout inspiration and expiration. Whereas normal subjects demonstrated a rather marked expiratory pause or relative bradycardia of 54 beats/minute or a 17% mean decrease ( $P < 0.0005$ ) patients decreased their rate only 4% to a mean rate of 79 beats/minute, an insignificant decrease ( $P > 0.05$ ). These highly significant differences of heart rate responses to a deep breath clearly separate patients with LHT from normal subjects.

While the normal phasic alteration of pulse rate with ventilation is known to lessen with age that was not felt to be an important consideration here because of the seven controls over age 42. Five decreased their expiratory pulse rate by 10% or more of the seven patients less than age 42; this degree of expiratory slowing was accomplished by only one.

Two particular precautions were observed. By performing the inhalation test a minimum of three times each effort being separated by at least eight to 10 heart beats possible variations ascribable to the slow vasomotor undulations of peripheral arterial pressure of Traube-Hering similarly reported in both sleep and wakefulness and extending considerably beyond a single respiratory cycle were minimized. Also the breath test performed in this study was rather rapid and deep but patients carefully refrained from gasping thus avoiding the associated peripheral vascular constrictive spinal reflex known to be unrelated to baroreceptor mechanisms but with

decreased handflow often lasting more than a minute and possibly influencing other vasomotor adjustments.<sup>12</sup>

A deficit of heart rate control during a deep breath in patients with LHT has not been previously reported and the associated pathophysiology must remain conjectural until more sophisticated study is applied. Interpretation of these mean group percentage changes must be tempered because the groups started from different resting heart rate baseline values. That this blunted responsiveness is suggestive of physiological uniqueness in LHT however is deduced from the observation that even in the three patients with resting heart rates less than the control average 57, 64 and 64 beats/minute each had an expiratory pause of far lesser degree 5, 5 and 2% than the control mean decrease of 17%. Additionally the two controls with resting rates greater than the patient average 86 and 91 beats/minute each had expiratory rate decreases 31 and 37% far greater than the patient mean decrease of 4%.

The higher resting pulse rate in LHT reported here has been well documented elsewhere and has been attributed to high indices of sympathetic nervous system activity,<sup>13</sup> low indices of parasympathetic cardiac inhibition,<sup>14</sup> and a resultant hyperkinetic circulation with enhanced myocardial contractility, high cardiac output and peripheral resistances adjusted excessively upward for any given cardiac output. Engrafted upon this abnormal milieu it would appear probable that several described neural and hemodynamic factors attendant upon taking a deep breath working separately or in concert are fundamental in producing the results reported here. Thus such an inspiration promptly increases venous return to the right heart with an increase in right ventricular stroke output of about 25%. As the associated increase in inspiratory capacity of the pulmonary vessels is more than sufficient to absorb the increase in right heart output an increment of blood is effectively withheld from the left ventricle with a resulting slight decrease in its size and of its stroke output by about 7%. This with the associated slight increase in volume capacity of the thoracic aorta in inspiration decreases systolic pressure with deep inspiration about 10% in normal subjects but as much as 30 mm Hg in patients with chronic



obstructive pulmonary disease. Heart rate similarly fluctuates with ventilation increasing about 5% with quiet ventilation but to as much as 30% in normal subjects during deep inspiration. This has been ascribed to the inspiratory aspiration of blood into the right heart activating the Bainbridge reflex to activation of baroreceptor mechanisms and to some spill over from the respiratory center into the vasomotor center with resultant phasic alteration of sympathetic and vagal efferent traffic to the heart. The final degree of heart rate increase and peripheral blood pressure decrease during inspiration and converse during expiration is the resultant vector of these several factors.<sup>1, 2, 3</sup>

Arterial baroreceptor dysfunction has been firmly established in hypertension and is expressed by shifting of response curves to the right with decreased sensitivity and upward resetting.<sup>4, 5</sup> While the intensity of the defect correlates with the duration of known hypertensive disease,<sup>6, 7</sup> some degree of resetting becomes established very early in hypertension certainly in less than days perhaps even hours and well before light or electron microscopic damage of arterial receptor sites,<sup>8</sup> suggesting to some its primacy in hypertension rather than involvement as a secondary phenomenon. This early loss of function without discernible structural change coupled with the fact that cardiac vagal efferent traffic ceases about 0.5 seconds before commencement of active inspiratory chest motion or phrenic nerve discharge,<sup>9</sup> suggests an important role for central factors.

In addition to this cessation of cardiac vagal activity inspiration causes an abrupt onset of pre and postganglionic sympathetic discharge activity at all spinal levels including cardiac renal and splanchnic sites. Perhaps this additional inspiratory adrenergic contribution was less influential among the LHT group reported here where basal sympathetic tone is already high thereby blunting the otherwise expected increase of heart rate with inspiration as reported here. Also to be considered however is the exaggerated degree of adaptive tachyphylaxis acting via a decreased number of active adrenergic receptors reported in the setting of a hyperadrenergic state as well as possible blunting of the aforementioned baroreceptor mechanisms in response to the stimulus of inspiration.

Expiration causes an abrupt enhancement of

cardiac efferent vagal traffic with only a brief central delay of 50 to 100 msec<sup>10</sup> and a reduction of visceral efferent sympathetic vasomotor activity.<sup>11</sup> Thus the expiratory pause in heart rate would appear to be predominantly a parasympathetic cardiac event and in the study reported herein disclosed even greater heart rate abnormalities in LHT than inspiration. This lends support to previous evidence of a severe impairment of cardiac parasympathetic innervation in LHT—an impairment similarly noted in sustained essential hypertension<sup>12</sup> and in a series of non hypertensive organic heart diseases.

Medullary and supramedullary influences markedly alter autonomic nervous system control of the heart and under certain experimental circumstances in animals can produce a state of borderline hypertension characterized by marked daytime pressure lability, rapid heart rate and circulatory hyperresponsiveness to such non noxious everyday stimuli as moderate noise, light and vibration—all rather suggestive of human LHT.<sup>13</sup> Whether this abnormal deep breath test reported here in LHT is reflective of such pathogenesis and whether this carries predictive significance concerning subsequent development of sustained hypertension awaits sophisticated study and long term prospective observation.

### Summary

A group of patients with borderline or labile hypertension were prospectively recruited and asked to take a deep breath while lying supine and being monitored by electrocardiography. Their attenuated heart rate responses were sharply abnormal demonstrating an excessively rapid rate throughout but without quickening on inspiration nor slowing with expiration. It is suggested that this further demonstrates inadequate autonomic control sympathetic and parasympathetic of the heart in labile hypertension and even at a moment when the patient's blood pressure is normal.

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# Effect of norepinephrine on coronary hemodynamics in coronary stenotic canine model

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Although the effect of norepinephrine on coronary hemodynamics has been studied utilizing a variety of experimental models<sup>1</sup> the coronary dynamic effect of norepinephrine in the presence of coronary arterial stenosis has received only limited study. Several studies have been directed at this question but have involved the systemic administration of norepinephrine.<sup>2-4</sup> Results thus obtained reflect both direct effects on the heart and the influence of systemic changes induced by norepinephrine. In order to evaluate the direct effect of norepinephrine in the presence of coronary artery stenosis we have studied the coronary dynamic effect of intracoronary administration of norepinephrine in the presence of partial coronary artery occlusion. We have found a significant decrease in coronary flow after norepinephrine in our canine model of coronary stenosis. In order to clarify the mechanism of decreased flow we subsequently studied the coronary response to norepinephrine in the stenotic model with prior alpha and beta receptor blockade. These studies suggested an interaction between the peripheral vasculature and the stenotic site

and further suggested that the stenosis was not fixed but rather was dynamic. In order to clarify the proposed mechanism two further studies were performed—administration of isoproterenol in the canine model and in vitro stimulation of the proposed interaction between stenosis and peripheral vasculature. In this paper we report our observations of an adverse effect of  $\beta$  adrenergic stimulation in the model of coronary artery stenosis which may exacerbate myocardial ischemia beyond that induced by an increase in myocardial oxygen demand.

## Methods

Animal studies were performed upon 22 mongrel dogs weighing between 29.5 to 34.1 kg. All animals were pretreated with morphine 1 mg/kg anesthetized with alpha chloralose 100 mg/kg and were mechanically ventilated. Supplemental doses of alpha chloralose were given as needed. Arterial blood PO<sub>2</sub>, PCO<sub>2</sub> and pH were periodically monitored throughout the experiment using a blood gas analyzer (Instrumentation Laboratory Model 113 Lexington Mass.) Respiratory adjustments and/or intravenous infusions of sodium bicarbonate were instituted when necessary to maintain pH between 7.3 and 7.45, PO<sub>2</sub> greater than 60 mm Hg and PCO<sub>2</sub> between 32 and 42 mm Hg. The heart was exposed through a left lateral thoracotomy and was suspended in a pericardial cradle. A catheter was advanced retrograde from the right femoral artery and positioned in the ascending aorta to

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measure aortic pressure. Coronary flow was measured with an electromagnetic flow probe (Biotronex BL610 Silver Springs Md.) Depending upon the coronary anatomy the flow probe was placed around the left anterior descending artery or the circumflex artery. If the left anterior descending artery was utilized the site of isolation varied from the proximal to the midportion of the artery. If the circumflex artery was utilized the site of isolation was proximal to the first major marginal branch.

A variable snare type occluder was placed distal to the flow probe. The snare consisted of a 1 mm wide band of Teflon passed around the artery through stiff tubing and attached to a machinist's micrometer. The snare could be closed by small precise amounts according to a 0.01 mm micrometer scale. Distal to the micrometer adjusted snare occluder a 1.0 silk suture was placed around the coronary artery. The ends of the suture were inserted through a piece of polyethylene tubing 3 cm in length. Zero flow was obtained 2 minutes after each norepinephrine or isoproterenol injection by pulling the ends of the suture while pressing on the polyethylene tubing against the coronary vessel. Calibration of the electromagnetic flow probe was performed by timed collections of blood in a graduated cylinder. Distal to the occluders a 22 gauge 1 inch angiocath (Deseret Pharmaceutical Co. Inc. Sandy Utah) was inserted into either a diagonal branch or directly into the circumflex artery. This catheter was utilized to monitor distal coronary arterial pressure. All norepinephrine or isoproterenol injections were through this cannula.

In the region perfused by the instrumented artery a small platinum electrode was inserted into the myocardium to measure an intramyocardial electrogram. In three animals wall motion was monitored by a mercury in silicone rubber segmental length gauge. Aortic pressure, coronary blood flow, coronary pressure distal to the snare, segmental wall motion and the intramyocardial electrogram were recorded on an Electronics for Medicine physiologic recorder Model DR8.

Distal coronary resistance was calculated by dividing mean distal coronary artery pressure by mean coronary blood flow. Stenotic resistance was calculated by dividing the mean pressure gradient across the stenosis by mean coronary flow. The mean pressure gradient across the

stenosis was calculated as mean aortic blood pressure minus mean distal coronary artery pressure. Pressure transducers were calibrated by manometer and were determined to be equally sensitive. Statistical analysis was performed by comparing the values prior to drug administration to the values obtained following drug infusion by Student's *t* test.<sup>10</sup>

All norepinephrine or isoproterenol injections were through the catheter used to monitor distal coronary arterial pressure. Norepinephrine or isoproterenol injections were of 1  $\mu$ g diluted to 1 ml with physiologic saline administered rapidly and followed by a flush of 0.5 ml physiologic saline. This quantity of physiologic saline did not have a measureable effect on coronary pressure or flow. All physiologic parameters were recorded continuously for a 10 minute period before and after the injection.

In seven dogs the effects of intracoronary injection of norepinephrine were examined before and after partial constriction of the coronary artery. Following the injection of norepinephrine in the unstenosed artery 30 minutes were allowed for recovery. Subsequently the snare occluder was gradually tightened until mean distal coronary pressure was reduced to approximately 60 mm Hg. After a 15 minute period to determine stability at this point norepinephrine was again injected.

In seven additional dogs the effects of intracoronary isoproterenol were examined before and after partial coronary artery constriction utilizing the methods outlined above.

In four dogs beta blockade was accomplished by administration of propranolol 1 mg/kg intravenously. The effects of norepinephrine were examined before and after partial constriction of the coronary artery as outlined above. In the remaining four dogs the effects of norepinephrine were studied after alpha blockade with phenoxyl benzamine 1 mg/kg intravenously again using the protocol outlined above. Beta blockade was verified by the failure of heart rate to change following an intravenous isoproterenol (5  $\mu$ g) injection at the beginning and end of the experiment. Alpha blockade was verified by the decrease in systemic arterial pressure following an intravenous epinephrine (2.5  $\mu$ g) injection at the beginning and end of each experiment.

All injections of norepinephrine were performed after the animal was observed to be stable

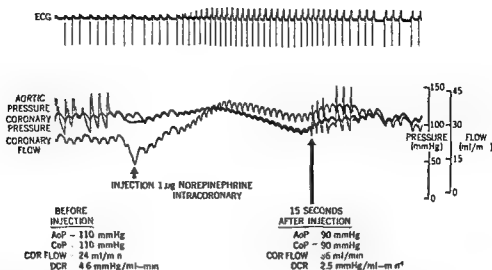


Fig 1A The coronary dynamic response to norepinephrine in the absence of coronary artery stenosis. An increase in coronary flow and decrease in distal coronary resistance (DCR) are demonstrated at 15 seconds after injection of norepinephrine.

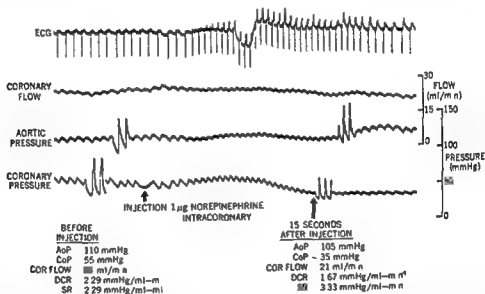


Fig 1B The coronary dynamic response to norepinephrine in the presence of coronary artery stenosis. A decrease in coronary flow and distal coronary pressure (CoP) and increase in stenotic resistance (SR) are demonstrated at 15 seconds after injection of norepinephrine.

over a 10 minute period. Measurement of parameters was made just prior to drug injection and at 7.5, 15, 30, 60, and 120 seconds after each injection.

To test if similar changes in stenotic resistance could be induced in vitro, a constant flow system was utilized. In five dogs the left and right carotid arteries were rapidly removed after killing the animal. The arteries were frozen in physiologic saline until they were studied. In each study after thawing the artery was attached to the perfusion system and stretched to its original

length. The artery was kept moist by externally applying physiologic saline. A Harvard syringe pump was utilized to maintain a constant flow at a rate of 22.9 cc per minute. The Harvard syringe pump was connected by tubing to the arterial segment (inflow). The other end of the arterial segment (outflow) was connected to tubing to which a rotating three way stopcock was attached. The stopcock had a 20 gauge (inner diameter 0.025 inch) cannula on one port and a 16 gauge (inner diameter 0.030 inch) cannula on another port. Flow through the stopcock could

Table I Coronary hemodynamic effects of norepinephrine

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/ml min)
<i>Before occlusion</i>				
Before norepinephrine	113.6 ± 4.4†	31.5 ± 2.5	3.80 ± 0.39	
After norepinephrine				
7.5 seconds	116.9 ± 5.0	35.3 ± 2.1	3.42 ± 0.30	
15 seconds	109.0 ± 4.7	36.4 ± 2.8	3.01 ± 0.27	
30 seconds	113.4 ± 5.0	32.9 ± 2.8	3.67 ± 0.40	
60 seconds	115.3 ± 4.0	30.7 ± 3.6	4.20 ± 0.58	
120 seconds	116.7 ± 3.4	30.3 ± 3.5	4.18 ± 0.54	
<i>After partial occlusion</i>				
Before norepinephrine	58.8 ± 1.3	29.8 ± 3.4	2.19 ± 0.70	2.04 ± 0.26
After norepinephrine				
7.5 seconds	51.0 ± 1.9	24.7 ± 3.3	2.20 ± 0.30	2.66 ± 0.42
15 seconds	38.8 ± 2.6	22.9 ± 3.6	2.01 ± 0.27	4.20 ± 2.66
30 seconds	37.5 ± 2.7	21.6 ± 3.9	2.13 ± 0.33	4.79 ± 1.16
60 seconds	40.6 ± 3.0	21.0 ± 4.1	2.60 ± 0.54	3.38 ± 1.55
120 seconds	39.7 ± 3.0	23.4 ± 5.2	2.28 ± 0.40	5.12 ± 1.53

Ch. 100 for m. pre. n. rep. n. ph. l. a. g. n. t. p. < 0.05 by Student's t test  
 All data are means ± t.d. r.d. r.o. of m. a. n.

then be directed through either a 20 gauge cannula alone (high peripheral resistance) or through both a 20 gauge and 16 gauge cannulae (low peripheral resistance). An isotonic dextran solution (17 centipoise) flowing from the syringe pump through the arterial segment would then have either high or low resistance outlets. A circumferential snare was placed around the arterial segment. Various degrees of stenosis were established with stenotic resistances varying between 10 and 60 mm Hg/ml min. Initial values were recorded during flow through the high resistance outlet. Pressures were recorded proximal and distal to the stenosed arterial segment. The stopcock position was then changed to allow flow additionally through the 16 gauge cannula needle simulating a low peripheral resistance. Proximal and distal pressures were again recorded. The stopcock was then closed allowing flow only through the 20 gauge Longwell needle. If the stenotic resistance or pressure gradient across the stenosis did not return to within 5% of the control value the data values were discarded.

## Results

Fig. 1 shows the typical response to norepinephrine. Prior to coronary artery constriction (Fig. 1A) norepinephrine caused a coronary blood flow increase and a distal coronary resistance decrease

After partial coronary artery constriction norepinephrine caused a strikingly different response (Fig. 1B). Distal coronary pressure and resistance decreased. Although the distal coronary resistance decreased the coronary blood flow decreased. This coronary blood flow decrease was associated with a large stenotic resistance increase. Table I summarizes the effects of intra-coronary norepinephrine (1 µg) in seven experiments. Prior to coronary artery constriction norepinephrine caused a slight coronary blood flow increase and distal coronary resistance decrease. After partial coronary artery constriction norepinephrine caused a marked decrease in distal coronary pressure and coronary blood flow. Distal coronary resistance decreased slightly. The coronary blood flow decrease was associated with a large stenotic resistance increase.

Table II summarizes the effects of intracoronary norepinephrine in four experiments after beta adrenergic blockade with propranolol. Prior to coronary artery constriction norepinephrine caused a significant coronary blood flow decrease and distal coronary resistance increase at 7.5 seconds. Beyond that point there were no significant changes. After partial coronary constriction norepinephrine caused a decrease in distal coronary pressure, coronary resistance at 7.5 seconds, and coronary blood flow decreased slightly. A

Table II Coronary hemodynamic effects of norepinephrine after beta adrenergic blockade

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/ml min)
<i>Before occlusion</i>				
Before norepinephrine	113.8 ± 3.2†	30.0 ± 0.7	3.83 ± 0.11	
After norepinephrine				
7.5 seconds	115.0 ± 3.6	22.0 ± 2.6	5.69 ± 0.81	
15 seconds	118.8 ± 2.7	33.2 ± 2.2	3.64 ± 0.30	
30 seconds	116.2 ± 3.2	29.6 ± 1.5	4.00 ± 0.20	
60 seconds	117.5 ± 4.1	28.1 ± 1.3	4.21 ± 0.12	
120 seconds	117.0 ± 4.1	29.0 ± 0.9	4.07 ± 0.09	
<i>After partial occlusion</i>				
Before norepinephrine	61.8 ± 1.0	2.4 ± 0.9	2.43 ± 0.10	1.93 ± 0.1
After norepinephrine				
7.5 seconds	88.8 ± 4.5	20.5 ± 2.5	4.16 ± 0.12	0.68 ± 0.3*
15 seconds	59.2 ± 4.1	23.8 ± 1.3	2.53 ± 0.21	1.88 ± 0.4
30 seconds	60.0 ± 5.9	23.7 ± 1.2	2.40 ± 0.2*	2.04 ± 0.49
60 seconds	60.0 ± 2.5	23.4 ± 1.4	2.61 ± 0.21	1.90 ± 0.34
120 seconds	63.8 ± 4.8	23.4 ± 0.9	2.50 ± 0.09	2.0 ± 0.3

Changes from pre-norepinephrine value significant at  $p < 0.05$  by Student's  $t$  test  
 All results are expressed as mean ± SEM

Table III Coronary hemodynamic effects of norepinephrine after alpha adrenergic blockade

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/ml min)
<i>Before occlusion</i>				
Before norepinephrine	107.5 ± 3.8†	42.7 ± 6.8	2.77 ± 0.48	
After norepinephrine				
7.5 seconds	100.0 ± 6.3	64.2 ± 12.1	1.77 ± 0.28	
15 seconds	99.5 ± 1.8	63.8 ± 9.1	1.63 ± 0.18	
30 seconds	113.0 ± 5.2	54.6 ± 7.6	2.70 ± 0.2†	
60 seconds	107.5 ± 6.5	47.1 ± 9.6	2.61 ± 0.49	
120 seconds	108.8 ± 6.2	40.4 ± 8.8	2.38 ± 0.38	
<i>After partial occlusion</i>				
Before norepinephrine	50.0 ± 2.0	30.2 ± 1.9	1.66 ± 0.15	1.40 ± 0.19
After norepinephrine				
7.5 seconds	51.8 ± 1.7	30.0 ± 2.9	1.73 ± 0.12	1.81 ± 0.19
15 seconds	44.2 ± 2.9	26.0 ± 1.5	1.70 ± 0.06	2.23 ± 0.61
30 seconds	39.5 ± 4.7	23.4 ± 2.2	1.53 ± 0.03	2.75 ± 0.41
60 seconds	39.2 ± 5.8	26.2 ± 0.3	1.71 ± 0.12	2.34 ± 0.26
120 seconds	42.3 ± 3.2	23.2 ± 1.8	1.72 ± 0.06	2.31 ± 0.6*

Changes from pre-norepinephrine value significant at  $p < 0.05$  by Student's  $t$  test  
 All results are expressed as mean ± SEM

decrease in stenotic resistance was encountered at the same time period. Thus beta adrenergic blockade by propranolol prevented the distal coronary pressure decrease and stenotic resistance increase that had occurred after norepinephrine.

Table III summarizes the effects of intracoronary norepinephrine in four experiments after alpha adrenergic blockade with phenoxybenzamine. Prior to coronary artery constriction, norepinephrine caused a large coronary blood flow increase and distal coronary resistance

Table IV Coronary hemodynamic effects of isoproterenol

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/ml min)
<i>Before occlusion</i>				
Before norepinephrine	173.6 ± 14	30.6 ± 1.0	42.5 ± 0.14	
After norepinephrine				
7.5 seconds	121.6 ± 14	107.3 ± 3.7	1.31 ± 0.0	
15 seconds	119.0 ± 2.1	100.5 ± 7.7	1.15 ± 0.04	
30 seconds	109.3 ± 9.5	60.3 ± 9.9	1.95 ± 0.04	
60 seconds	119.6 ± 1.6	39.9 ± 1.7	3.74 ± 0.17	
120 seconds	177.9 ± 1.4	33.4 ± 1.1	3.89 ± 0.14	
<i>After partial occlusion</i>				
Before norepinephrine	63.5 ± 1.2	20.8 ± 0.4	3.05 ± 0.04	3.01 ± 0.29
After norepinephrine				
5 seconds	46.1 ± 2.3	19.0 ± 0.9	2.57 ± 0.11	6.11 ± 0.94
15 seconds	38.9 ± 1.4	16.6 ± 0.9	2.60 ± 0.13	6.28 ± 1.54
30 seconds	35.6 ± 1.9	14.7 ± 1.0	2.58 ± 0.13	6.89 ± 1.33
60 seconds	35.4 ± 2.3	17.1 ± 1.0	2.91 ± 0.15	7.81 ± 1.33
120 seconds	39.0 ± 2.1	13 ± 1.0	3.27 ± 0.20	8.92 ± 2.46

p &lt; 0.05 compared from pre-injection value Student's t test

\*All data are mean ± standard error of mean

Table V Effects of peripheral resistance changes on stenotic resistance in an in vitro constant flow stenosed carotid artery preparation

Peripheral resistance (mm Hg/ml min)	Peripheral pressure (mm Hg)	Distal pressure (mm Hg)	Stenotic resistance (mm Hg/ml min)
5.18 ± 0.04†	155 ± 4	118.5 ± 1.4	1.60 ± 0.10
0.0 ± 0.02	164.4 ± 18.5	16.1 ± 0.4	6.47 ± 0.62

p &lt; 0.01 compared from control by Student's t test

†All data are mean ± standard error of mean

decrease. After partial coronary artery constriction, norepinephrine caused a large distal coronary pressure decrease and a slight decrease in the distal coronary resistance. Although the distal coronary resistance decreased, the coronary blood flow decreased. This coronary blood flow decrease was significantly ( $p < 0.05$ ) different from the response to norepinephrine in the animals without stenosis and was associated with the stenotic resistance increase. Thus, alpha adrenergic blockade by phenoxylbenzamine did not prevent the distal coronary pressure decrease and stenotic resistance increase that occurred after norepinephrine.

Mean aortic pressure and heart rate did not change significantly following norepinephrine in any of the above groups.

Table IV summarizes the effects of intracoronary isoproterenol in seven experiments and represents further evidence for a beta receptor mediated response as the mechanism for the changes seen following norepinephrine. Prior to coronary artery constriction, isoproterenol caused a large coronary blood flow increase and a coronary resistance decrease. After partial coronary artery constriction, isoproterenol caused a large distal coronary pressure decrease and a slight distal coronary resistance decrease. Although the distal coronary resistance decreased, the coronary blood flow decreased. This coronary blood flow decrease was significantly ( $p < 0.05$ ) different from the normal response to isoproterenol and was associated with a large stenotic resistance increase. In this group, mean aortic



pressure was unchanged but heart rate increased significantly following isoproterenol

Table V suggests that the stenotic resistance changes are related to alteration of peripheral coronary resistance and intraluminal changes in pressure. Table V summarizes the results of the in vitro constant flow experiments and is based upon 51 observations in seven arteries. Lowering the peripheral resistance in a constant flow system caused an obvious reduction in the distal pressure. Reducing the distal pressure always caused stenotic resistance to increase. This stenotic resistance increase caused the proximal pressure to increase, although the peripheral resistance had been greatly reduced. Further these stenotic resistance changes were bidirectional: lowering the distal pressure increased the stenotic resistance while increasing the distal pressure decreased the stenotic resistance.

## Discussion

The effect of norepinephrine administered into the unobstructed coronary artery reflects both alpha and beta adrenergic receptor responses.<sup>11</sup> The net effect in our study was a slight transient decrease in coronary vascular resistance followed by a minimal increase in resistance at one to two minutes following injection. These findings are similar to those reported by others and are presented primarily for the purpose of comparing the coronary vascular response to norepinephrine before and after partial coronary artery constriction. In the setting of severe partial coronary artery constriction, dramatic differences in response were noted. Thus following intracoronary administration of norepinephrine a decrease in coronary blood flow and distal coronary pressure with an increase in stenotic resistance were documented. This response was not seen following pretreatment with propranolol suggesting beta receptor stimulation as the mediator of this response. Alpha adrenergic blockade with phenoxybenzamine did not alter this response. Further beta adrenergic stimulation with isoproterenol caused a similar decrease in coronary blood flow and distal coronary pressure and an increase in stenotic resistance.

Several potential mechanisms for the observed stenotic resistance increase after norepinephrine were not substantiated by our findings. We initially considered the possibility of an alpha

adrenergic induced vasoconstriction at the snare. However, in animals pretreated with propranolol the alpha adrenergic response manifested as an increase in coronary pressure, decrease in coronary flow, and decrease in peripheral resistance (Table II). These changes were only transient with a peak noted at 75 seconds and with subsequent return to control values. Thus there was no increased stenotic resistance in this group of animals. Furthermore, the phenoxybenzamine pretreated animals had a response similar to that of the animals without adrenergic blockade. Alpha adrenergic stimulation is thus unlikely to be the mechanism of the coronary flow decrease and stenotic resistance increase.

An increase in turbulence consequent to epinephrine was also considered. After epinephrine and isoproterenol coronary blood flow decreased while stenotic resistance increased. The presence of decreased flow is thus consistent with the hypothesis that an increase in turbulence is the cause for the observed stenotic resistance changes.<sup>11</sup>

A decrease in systemic pressure in the presence of a critical stenosis could also result in a decrease in flow and distal pressure. However, such a decrease in systemic pressure was not demonstrated. A change in collateral supply to the distal to the stenosed artery might also be considered to mediate the observed changes. However, potential changes in collateral blood flow would occur in the distal coronary vessels and therefore could not account for the observed changes in stenotic resistance and decreased antegrade coronary flow.

It is of note that the stenotic resistance changes were also observed in an in vitro carotid preparation. This finding is in support of a primary role for the alteration in distal pressure as a primary cause for the stenotic resistance changes. Although the flow rate was constant, stenotic resistance changes were bidirectional. Lowering the distal pressure and resistance increased the stenotic resistance while increasing the distal pressure and resistance decreased the stenotic resistance (Table V). This suggests that the stenosis was not fixed but was subject to dynamic alteration related to hydraulic phenomena. It also suggests that unlikely phenomena such as platelet

gation alteration of collateral flow and alteration in flow turbulence were the primary cause for the observed changes in stenotic resistance.

We postulate that the initiating event following norepinephrine administration is a beta<sub>1</sub> and/or beta<sub>2</sub> adrenergic mediated decrease in arterial tone leading to an alteration of geometry at the stenotic site. Because of proximal high grade narrowing of the coronary artery flow cannot increase *pari passu*. A coronary pressure decrease thus results. The norepinephrine induced decrease in distal coronary pressure will result in a decrease in pressure by the stenosis according to Bernoulli's equation. This decrease in intraluminal pressure may then lead to a decrease in the effective stenotic area. In the presence of an underlying high grade stenosis a minimal decrease in radius will be sufficient to significantly increase stenotic resistance. The concept of a passive change in stenotic resistance has been previously described by Schwartz and co workers. In addition Logan has demonstrated in *in vitro* perfused human arteries that vessels with eccentric lesions demonstrate a variable resistance to flow. Resistance to flow was inversely related to the perfusion pressure; the lower the perfusion pressure the higher the resistance.

We have previously demonstrated in the model of coronary stenosis that another stimulus of distal coronary vasodilation transient occlusion of the vessel resulted in a decrease in coronary flow and an increase in stenotic resistance. *In vitro* studies with two types of tubing revealed that these changes were seen with relatively flexible but not with relatively rigid tubing. These findings suggested that with some mobility of a portion of a tight stenosis the stenosis demonstrated dynamic rather than fixed hydrodynamic consequences.

We are unable to further confirm the mechanisms we have suggested since the changes in radius which may occur at the stenotic site are beyond the resolution of our current angiographic techniques. Nonetheless although we cannot conclusively confirm the mechanisms we have suggested the observation of a coronary flow and pressure decrease and a stenotic resistance increase following norepinephrine demonstrates an adverse effect of beta adrenergic stimulation which may further exacerbate ischemia beyond that induced by an increase in myocardial

contractility and an increase in myocardial oxygen demand. Prevention of this phenomenon by propranolol is of interest in assessing the mechanism of its development. Furthermore it also suggests that in the presence of coronary stenosis propranolol may decrease myocardial ischemia by maintaining coronary flow and pressure in addition to its well recognized mode of action of decreasing myocardial oxygen demand.

In conclusion we have documented the response of the coronary vasculature to norepinephrine in the presence of a critical coronary arterial narrowing. The response to such intervention mediated by beta adrenergic stimulation results in a significant decrease in coronary flow. An increased resistance at the stenotic site is suggested as the likely mechanism. This phenomenon may be of importance in the pathophysiology of coronary artery disease.

### Summary

The effect of intracoronary injection of 1 µg norepinephrine was assessed in 14 open chest dogs anesthetized with alpha chloralose. Studies were performed before and after partial coronary artery constriction by a circumferential snare. Aortic pressure, coronary pressure distal to the stenosis and coronary flow were monitored before and after injection of norepinephrine. Calculated values were stenotic resistance and distal coronary resistance. Before coronary constriction norepinephrine resulted in an early minimal increase in coronary flow and decrease in distal coronary resistance with prompt return to control values. In contrast with high grade coronary constriction at 15 seconds after norepinephrine coronary flow decreased ( $29.8 \pm 3.4$  to  $22.9 \pm 3.6$  ml/minute) ( $p < 0.05$ ), coronary pressure decreased ( $58.8 \pm 1.3$  to  $28.8 \pm 2.6$  mm Hg) ( $p < 0.05$ ), and stenotic resistance increased ( $2.04 \pm 0.26$  to  $4.20 \pm 2.66$  mm Hg/ml min) ( $p < 0.05$ ) without change in heart rate or aortic pressure. These changes persisted over a two minute period of observation following norepinephrine. In the stenotic model the decrease in coronary pressure and coronary flow and increase in stenotic resistance were blocked by pretreatment with propranolol but not by phenoxbenzamine. Administration of isoproterenol resulted in changes similar to those induced by norepinephrine in the stenotic model. Simulation of

alteration of peripheral resistance in an in vitro model demonstrated that with a high initial stenotic resistance a decrease in peripheral resistance resulted in an increase in stenotic resistance. We conclude that the decrease in coronary pressure following norepinephrine was mediated by beta<sub>1</sub> or beta<sub>2</sub> adrenergic stimulation. We further postulate that the decreased coronary flow and increased stenotic resistance were caused by a passive decrease in radius at the stenotic site.

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## Case reports

### Superior vena cava syndrome Case report

A complication of permanent transvenous endocardial cardiac pacing requiring surgical correction

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Thromboembolism of the great veins is an unusual but well documented complication of transvenous endocardial pacing. The condition may present as superior vena cava syndrome and such cases have previously responded to conservative management. However, because of concern about the nature of the lesion and the progression of symptoms in this case, surgical intervention was chosen.

#### Case report

A 75-year-old woman had a transvenous endocardial pacemaker inserted in 1973 on account of Stokes-Adams attacks. In November 1977 she developed painless swelling of her face and upper limbs which increased over the ensuing months. When she presented in March 1978 her facial and limb swelling were considerable (Fig 1). Cyanosis of her thorax, arms and head in association with hoarseness and altered mentation had also appeared in the weeks prior to admission.

Examination revealed the mucous membranes of her face to be suffused and macroglossia to be present. Telangiectasia was present in the skin over the upper trunk. Her neck veins were grossly distended as were the veins in the arms and chest wall. Fundoscopy likewise showed venous distension. Physical examination was otherwise unremarkable apart from the presence of a short ejection systolic murmur in the aortic area.

Laboratory investigations demonstrated normal blood count and biochemistry. The electrocardiogram showed incomplete right bundle branch block and satisfactory demand mode of pacemaker function. Chest x-ray showed slight widening of the upper mediastinum but tomography



Fig 1 Preoperative photograph demonstrates marked facial edema. Note imprint from spectacle frame.

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and gallium scan failed to demonstrate any specific mediastinal lesion. Under fluoroscopy however the pacemaker lead did not exhibit the usual sling-like action at the superior cavo-atrial junction and appeared to be fixed at this point. Superior and inferior vena caval catheterisation demonstrated a shelf-like obstruction of the superior vena cava at its junction with the right atrium (Figs 2a and 2b). A pressure



Fig 2 A and B PA and lateral superior vena cavogram demonstrating stenosis at superior cavoatrial junction

gradient of 26 mm Hg was measured between the superior vena cava and right atrium

In view of her age transvenous dilatation of the obstructing lesion was attempted in the first instance. However although a balloon catheter could be placed with difficulty within the obstructing segment the obstruction itself was too rigid to allow dilatation by balloon inflation. Since she was becoming increasingly symptomatic with facial edema and because of concern about possible cerebral thrombosis surgery was recommended.

At operation the heart was exposed through a median sternotomy incision. The superior vena cava appeared and felt normal apart from venous hypertension; an obvious tumor mass however could be palpated in the upper third of the atrium. The patient was connected to cardiopulmonary bypass by cannulation of superior and inferior venae cavae and ascending aorta. On opening the right atrium the lumen between the right atrium and superior vena cava was seen to be obliterated by a firm tumor with the catheter which passed the endocardial pacer hole in the right atrium was made through the tumor down to the right ventricle. A portion of the tumor like mass was excised. Histological examination of the lesion showed myocardial hypertrophy and fibrous tissue and a surface layer of fibrin thrombus. There was no evidence of malignancy.

To ensure an adequate lumen the pericardium was placed over the graft onto the lateral atrial wall. Pressures were measured at the site of the lesion at the end of the operation and a

gradient could be detected. The transvenous lead was and was replaced with an epicardial lead.

The patient made an uneventful recovery from the operation and was discharged home two weeks later relieved of symptoms. She remains well (follow up 6 months).

### Comment

The more common complications of pericardial transvenous endocardial pacing include lead dislodgement, generator pocket infection, lead dislodgement, cardiac perforation, and lead fracture. Thromboembolism related to the lead occurs rarely but four cases have previously been reported where the venous thrombosis manifested as superior vena cava syndrome. All the cases resolved with anticoagulant therapy with one instance streptokinase was used for long term anticoagulation.

The use of anticoagulant or thrombolytic therapy would not have effected a cure in our case since the bulk of the obstructing lesion consisted of fibrous tissue. This was considered to represent an unusual tissue response of the endocardium to chronic irritation by the transvenous pacer lead and with removal of the irritant



Fig 3 Histology of resected specimen demonstrating myocardium with adjacent fibrotic tissue and surface fibrin deposition

was effected with little chance of recurrence

We believe this to be the first report of a fibrotic endocardial lesion associated with an endocardial pacemaker lead manifesting as superior vena cava syndrome

### Summary

Superior vena cava syndrome developed in a patient in whom an endocardial transvenous pacemaker had been inserted five years previously. Venography demonstrated an obstructing lesion at the junction of the superior vena cava and right atrium. Balloon catheter dilatation failed to afford any relief from her progressive symptoms. Exploration of the area revealed a

benign fibrotic lesion encircling the pacemaker lead within the right atrium. Excision of the lesion, removal of the lead, and patching the right atrium with pericardium resulted in rapid cure.

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## Multiple coronary thromboses in previously normal coronary arteries: a rare cause of acute myocardial infarction

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Most acute myocardial infarcts are associated with atherosclerotic narrowing of the coronary arteries although occasional and relatively infrequent instances of infarction with normal coronary arteries have been described.<sup>1</sup> Acute coronary occlusions are most often caused by thrombosis overlying an eroded atherosclerotic plaque but thromboemboli may be a source of acute occlusion of an otherwise normal coronary tree. Described here is an unusual patient with previously normal coronary arteries who developed acute thrombosis of the proximal right and left anterior descending coronary arteries which led to a fatal myocardial infarction. The role of heparin in the pathogenesis of the coronary thrombi in this particular patient is suggested.

### Case report

A 44 year old woman with a history of cigarette smoking and mild hypertension was admitted to the hospital for evaluation of vertigo and dysarthria. She had been well until one month previously when she developed daily frontal and occipital headaches which occurred upon awakening. The headaches would resolve as the day progressed and were

associated with any visual or neurologic symptoms. She, before admission, she felt the room spinning from right to left, noted visual blurring and a three minute period of slurred speech. Her family history was positive for diabetes, hypertension and myocardial infarction. She was on no medications.

Physical examination on admission revealed a temperature of 99.2°F, a pulse of 76 which was regular and a blood pressure of 124/80. Cardiovascular examination was normal without murmurs, rubs or gallops. Neurologic examination was normal except for horizontal nystagmus and mild left-sided facial weakness. Laboratory values on admission included a normal complete blood count with a platelet count of 243,000. Chemistries were normal except for a total cholesterol of 279. The chest radiograph and electrocardiogram were normal. A lupus erythematosus cell preparation and rheumatoid factor were negative.

**Hospital course.** Shortly after admission a lumbar puncture and CAT scan (computerized axial tomography of brain) were normal. Carotid arteriography showed a stenosis of the left internal carotid artery 7 cm above bifurcation but due to a radiographic contrast reaction the right system was not studied. With a diagnosis of transient ischemic attacks intravenous heparin was instituted and 36 hours later was complete resolution of her neurologic symptoms. On the tenth hospital day her platelet count was 43,000 and heparin was discontinued. Within a matter of hours she developed crushing retrosternal and back pain. The electrocardiogram showed changes of an acute inferior myocardial infarction. The patient was transferred to the coronary care unit. A repeat platelet count was 1,000 but post-thromboplastin and prothrombin times were not abnormal. Over the next 24 hours she became hypotensive and developed electrocardiographic changes of anterior myocardial infarction. The patient developed refractory ventricular fibrillation and died 24 hours after her first episode of chest pain.

**Autopsy findings.** At autopsy her heart weighed 340 gm. An acute myocardial infarct was present in the anterior wall of the left ventricle extending into the septum.

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and involving a substantial amount of the right ventricle. Postmortem coronary arteriography demonstrated occlusion of the left anterior descending coronary artery and the right coronary artery (Fig 1) and fresh thrombus was present in both vessels at the sites of occlusion. Histologic examination of the thrombus showed evidence of organization compatible with 12 to 24 hours (Fig 2). There was no arteritis or congenital abnormality of the coronary tree. The remainder of the coronary arteries were widely patent without evidence of significant atherosclerosis. Examination of the brain showed no hemorrhages, infarcts, or vascular abnormalities. In situ examination of the carotid arteries revealed 50% stenosis of both right and left internal carotid arteries. The remainder of the autopsy was unremarkable without evidence of systemic vasculitis or thrombotic lesions elsewhere either in the systemic arteries or in the pulmonary vessels.

### Discussion

This relatively young woman died of a massive myocardial infarction that involved well over half of her left ventricle and a significant portion of the right ventricle. The infarcts occurred in a heart with previously normal coronary arteries in which sudden and apparently simultaneous occlusions of both right and left coronary arteries occurred. Her rapidly progressive downhill course with cardiogenic shock and heart block was compatible with the extensive myocardial injury. The most peculiar feature of her coronary lesions however was that they were due to thrombotic occlusions of the proximal vessels unassociated with underlying atherosclerosis, intimal plaque rupture, or other arterial lesions such as vasculitis which might account for the thrombosis.

The cause of acute thrombosis in this patient is not entirely clear. The most common cause of a thrombotic occlusion of a previously normal coronary artery is embolization. Almost always however a source of the embolus can be identified whereas in this patient there was no evidence of thrombotic material on the heart valves or mural endocardium. Her coronary lesions were also unusual for embolic phenomena in that both were proximal in location. Coronary emboli in three quarters of instances lodge distally in the previously normal coronary vessel and cause generally small although transmural infarcts. The massive and fatal myocardial injury in this woman was due to the proximal location of both coronary occlusions leading to loss of most of her left ventricle. Also unusual for embolization is the simultaneous involvement of two main coronary vessels. Without atherosclerosis, intimal injury, vasculitis, or a source of embolization, one must consider that *in situ* thrombosis of



Fig 1 Postmortem angiogram showing occlusive lesions in left anterior descending (LAD) and right coronary arteries (RC). By the time of death thrombi in both vessels had retracted restoring flow to the distal vessels. The coronary vessels are otherwise widely patent and free of disease.

her coronary arteries may be related to the heparin therapy.

Coronary artery spasm is a known etiology of myocardial infarction in patients with normal coronary arteries. There is at least one documented case in which at autopsy a fresh thrombus was found at the site of angiographically proven spasm, and it was suggested that blood stagnation may have resulted in platelet aggregation, release of thromboxane A and thrombus deposition at the site of spasm. There are however several points which make spasm an unlikely precipitating cause of our patient's multiple thrombi. All of the patients with a vasospastic explanation for myocardial infarction had multiple attacks of angina before the infarction, whereas our patient had no history of chest pain. Of over 200 patients reported with angiographically documented spasm, only one had evidence of spasm involving two major coronary arteries. Also if spasm leads to coronary thrombosis via the release of thromboxane A from platelets, one might question whether this hypothesis is valid.



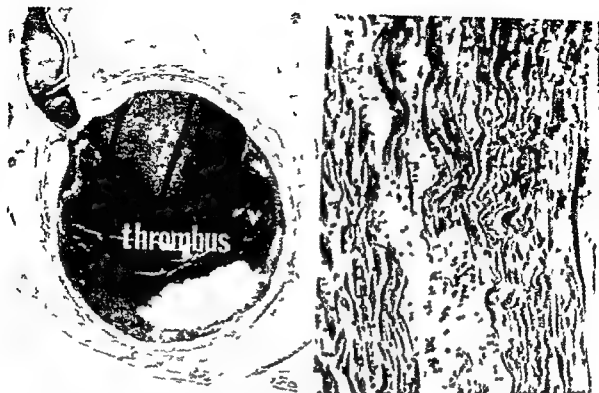


Fig 2 Shown on the left is a transverse histologic section from the left coronary artery showing the thrombus within the lumen. The thrombus has partially retracted and angiographic injection mass is seen above it. The coronary vessel is free of atherosclerosis. Shown on the right is a section of infarcted left ventricular myocardium in the distribution of the occluded vessel. The thin wavy fiber change and polymorphonuclear infiltrate are compatible with an infarct of 24 hours of age (Hematoxylin and eosin original magnifications—left  $\times 43$ , right  $\times 175$ )

a patient with thrombocytopenia. Thus although we cannot exclude a vasospastic myocardial infarction in our patient we believe this is unlikely.

There is a precedent for thromboembolic phenomena occurring on heparin therapy. In 1958 Weismann and Tabin reported 10 cases of peripheral vascular emboli in heparinized patients over a three year span. These patients received heparin 150 to 500 mg per day intramuscularly and at autopsy there was no evidence of a cardiac source for the emboli. Roberts and colleagues in 1964 studied 11 cases of surgically proved peripheral emboli in patients on heparin for at least ten days. Barker studied 110 cases of arterial emboli and suggested that 12% were induced by heparin therapy. Rhodes reported two patients similar to ours who developed myocardial infarction associated with heparin administration. Both patients were receiving heparin for thrombophlebitis and had no prior history of cardiac disease. On day eight and day ten of heparin therapy respectively these patients had clinical and electrocardiographic

changes consistent with myocardial infarction and survived. It was postulated that increased platelet aggregation and adhesiveness were the cause of the myocardial infarctions. Thus, of the multiple reports of heparin associated vascular thromboemboli we have identified only two patients who have been reported to develop acute myocardial infarction while on heparin for noncardiac reasons. Both infarctions occurred after eight days of therapy and were seen in patients who were thrombocytopenic. In these latter two patients however angiographic or morphologic confirmation of the coronary lesions was not obtained and whether acute thrombosis within the coronary tree occurred or not known.

These three patients with myocardial infarction in the setting of thrombocytopenia and heparin therapy at least raise the suspicion that the two together or alone related to the infarction. One considers how vascular thrombosis can occur on heparin therapy. It is always possible that inadequate anticoagulation was achieved, especially in between doses. Another possibility may be related to the thrombocytopenia.

disseminated intravascular coagulation that may develop on heparin therapy.<sup>1</sup> Bell and co-workers have identified a phenomenon of diffuse intravascular coagulation and thrombocytopenia found in patients on heparin. This tends to occur between day 2 and 10 of heparin therapy and takes 2 to 5 days to resolve after heparin is discontinued. Although this reaction to heparin has been associated with hemorrhagic problems, no documented thrombosis or embolization have occurred. If this indeed represents a diffuse intravascular coagulation type of state, it would not be surprising to identify thrombotic events in these patients. In an autopsy study of diffuse intravascular coagulation from other causes, Sugura and associates found a 20% incidence of coronary thrombosis and a 16% incidence of myocardial infarction. It may well be possible therefore that the acute myocardial infarction and acute coronary thrombosis in previously normal coronary arteries that occurred in our patient in association with heparin treatment were a manifestation of coagulopathy. That her chest pain occurred within hours of stopping heparin might also suggest a rebound phenomenon from the effects of anticoagulant. There is little evidence, however, that a rebound hypercoagulable state can develop as a consequence of anticoagulant withdrawal.<sup>1</sup> Whatever the mechanism, one cannot ignore the association of heparin thrombocytopenia with her unusual thrombotic event.

More importantly, this case does show that the coronary arteries may be a site for acute thrombosis without underlying atherosclerosis, arteritis, or other vascular pathology. Such a case at least raises the possibility that coagulation abnormalities may be responsible for some forms of acute myocardial infarction and that infarcts can occur, albeit rarely, in patients with previously normal coronary arteries.

### Summary

This report describes an unusual form of myocardial infarction in a 44-year-old woman who was found to have two proximal coronary artery thrombi with otherwise normal coronary

arteries. An interesting feature of her history was that the coronary events occurred in association with thrombocytopenia and heparin treatment. Two other clinical reports of patients who developed thrombocytopenia and myocardial infarction while receiving heparin have been identified,<sup>1</sup> and the possibility that these thrombi were secondary to a coagulation abnormality associated with heparin is considered.

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The electrocardiogram demonstrated a mean frontal plane P axis of  $+170$  degrees with a mean frontal plane QRS axis of  $-90$  degrees (Fig 1). A PR interval of 0.16 sec. prolonged for a patient of this age was recorded. Although far right chest leads were not obtained the available leads

From the inferior vena cava the catheter was advanced, very likely through an interatrial communication into the superior vena cava which is on the right side. Injection was made into this superior vena cava (Fig. 4). This resulted in dense opacification of an atrium with comma shape and atrial appendage which is located to the right of the superior vena cava and is positioned anteriorly. The shape and course of the atrial appendage indicates an anatomical left atrium. There is faint opacification of another atrium as well. There is dense opacification of the ventricle as seen in Fig. 3 but the source of flow into this ventricle is uncertain.

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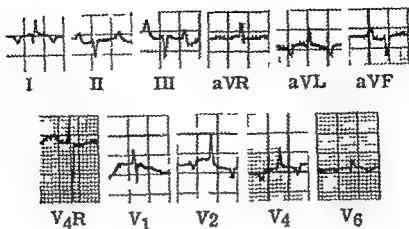


Fig 1 Electrocardiogram

In this case the situs was very difficult to determine because in situs inversus with left aortic arch the descending aorta should cross the midline in the lower thorax and be located in the abdomen to the right of the spine. Unfortunately the abdominal aorta was not clearly seen in the frontal projection of the angiocardiogram. Similarly, in situs inversus the superior vena cava should be on the left rather than on the right side; this is not the case here (Fig 4a). On the basis of the films that are available it is very likely that this patient has a situs indeterminus (abdominal heterotaxia) with dextroversion of the heart. The congenital anomaly, as judged by angiography, is compatible with single ventricle with transposition of the great vessels and atresia of the pulmonary artery. There is a patent left ductus arteriosus. Two atria are present with very likely the right superior vena cava entering directly into a right-sided anatomic left atrium.

DR EPSTEIN: Thank you, Dr Formanek. During cardiac catheterization the following facts were elicited:

There was a persistent right superior vena cava draining into the right-sided atrium. Pulmonary atresia was discovered with pulmonary blood flow depending on a patent ductus arteriosus. The patient underwent a right subclavian to pulmonary artery anastomosis (Blalock-Taussig shunt). The postoperative course was uncomplicated.

The infant again presented to the University of Minnesota Hospitals at about 4 months of age with a 2 to 3 week history of irritability and mild symptoms of upper respiratory disease. He suffered a sudden hypotensive cardiorespiratory arrest and died shortly after readmission.



Fig 2 Frontal view of thoracic roentgenogram

Dr Bessinger: Will you present the differential diagnosis?

DR BESSINGER: This case presents a common problem to the cardiologist seeing neonates: namely, persistent cyanosis. There is the interesting finding of dextrocardia in association with apparent situs inversus. The infant was of normal size following an unremarkable pregnancy; therefore, diseases affecting the premature infant do not immediately come to mind. The key fact in the presentation is the persistence of generalized cyanosis that was unresponsive to high  $\text{FiO}_2$ , as evidenced by the  $\text{pO}_2$  of 35 torr while inspiring 80 per cent oxygen. The other key fact is the chest x-ray, which showed the cardiac silhouette to be enlarged and the pulmonary vascularity to be

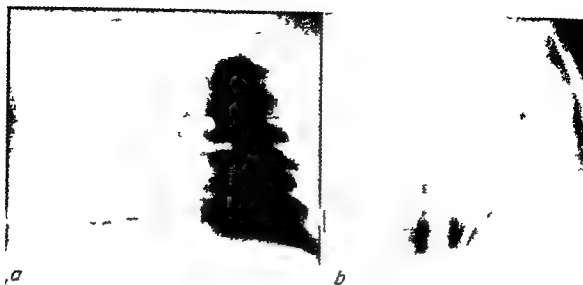


Fig 3 Ventriculography after the catheter had passed into the heart through a left sided inferior vena cava. Frontal view *b* Lateral view



Fig 4 Angiocardiograms made after passing the catheter through the left sided inferior vena cava then through the atrial portion of the heart and into a right sided superior vena cava. Injection made into latter *a* Frontal view *b* Lateral view

decreased. This combination of persistent arterial hypoxemia in spite of increased  $\text{FiO}_2$  and decreased pulmonary vasculature leads one to a consideration of congenital cardiac lesions that cause obstruction to pulmonary blood flow with right to left shunting. These lesions are compatible with intrauterine circulation but become very obvious once the infant is delivered and is dependent upon his own pulmonary blood flow for adequate arterial oxygenation. In this group are Ebstein's anomaly, transposition and pulmonary atresia (or severe pulmonary stenosis) ei-

ther with intact ventricular septum or with ventricular septal defect. The cardiac examination showed findings that are compatible in the first heart sound was normal and the second heart sound was increased and single. This finding suggests the absence of one semilunar valve and perhaps anterior displacement of the aorta. The 3/6 cardiac murmur was compatible with a patent ductus arteriosus and interest was heard best along the right sternal border. Physical examination suggested the "wink" in this case in that the liver was palpable on the

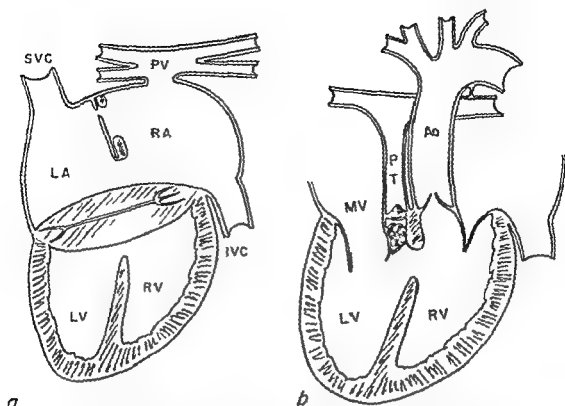


Fig 5 Essentials of the intracardiac structures. *a* Detailing the atrial connections and ventricles. The anatomic right atrium (RA) lies on the left side and receives the pulmonary veins (PV). The anatomic left atrium (LA) lies on the right side and receives a right sided superior vena cava (SVC). There is a large atrial septal defect in the lowermost part of the atrial septum beneath which is a common atrioventricular valve. Beneath the latter is an interventricular communication. The inferior vena cava (IVC) lies on the left and joins the anatomic right atrium. The ventricles are inverted. The anatomic right ventricle (RV) lies on the left and the anatomic left ventricle (LV) lies on the right. *b* Details of the ventricular connections. The inverted right ventricle (RV) leads to a transposed aorta (Ao) while the pulmonary trunk (PT) arises from the inverted left ventricle (LV). The pulmonary valve is atretic and the subpulmonary zone is obstructed by accessory endocardial tissue. MV = inverted mitral valve.

side and the cardiac impulse was palpable over the right chest. Thus from the physical examination, the chest x ray and the persistent cyanosis one is led to the fact that the child is ductus dependent and therefore has some type of congenital lesion resulting in severe or total obstruction to pulmonary blood flow from the heart.

In considering the chest x ray the finding is that of complete situs inversus. While patients may have complete situs inversus of thoracic and abdominal viscera and have completely normal hearts, the incidence of cardiac disease has been estimated to be increased to 3 to 9 per cent and in those with cardiac disease 80 per cent have been reported as having the cyanotic type of congenital disease. The chest x ray findings do not suggest the situation where situs is indeterminate as in the asplenia and polysplenia syndromes. The x ray findings of an enlarged heart in association

with decreased vascularity suggests Ebstein's anomaly, tricuspid atresia or pulmonary atresia with intact septum as opposed to the more usual picture of normal cardiac size in pulmonary atresia with ventricular septal defect (tetralogy of Fallot).

The electrocardiogram is interesting in that the P wave axis is toward the right and inferior compatible with a situs inversus of the atria. The frontal plane QRS axis of minus 90 degrees is interesting. If the patient had situs solitus and an axis of minus 90 degrees, endocardial cushion defect would come immediately to mind. The chest leads did not include complete right chest leads. A diagnosis of right ventricular hypertrophy on the electrocardiogram would be helpful in that it would be evidence against an Ebstein's anomaly or tricuspid atresia. On the other hand the presence of right atrial enlargement on the



Fig 1 a Anterior view of thoracic organs. The apex of the heart points toward the right and the aorta (A) is the more anterior of the two vessels. Each lung has three lobes (U = upper M = middle L = lower) LAD = left anterior descending coronary artery. b Posterior view of thoracic organs showing confluence of pulmonary veins (PVC) from which through an orifice (probe) the confluence of pulmonary veins leads into the left-sided anatomic right atrium (RA). LA = right-sided anatomic left atrium. c Left-sided anatomic right ventricle (RV) leading to the aorta (A). d The right-sided anatomic left ventricle (LV) and pulmonary trunk (PT). The pulmonary valve (V) is atrial and dome-shaped while beneath the valve is accessory tissue (M) which causes subpulmonary stenosis. Inferior to this lies the mitral valve which is in fibrous continuity with the pulmonary valvular tissue.

electrocardiogram would be compatible with each of these conditions.

In the report of Stanger and associates, on necropsy specimens showing cardiac malpositions 13 cases had complete situs inversus. In three the hearts were normal. In the remaining ten cases there were various types of anomalies

six having pulmonary stenosis (or pulmonary atresia). Interestingly, one patient was reported as having a persistent common atrioventricular canal.

The echocardiogram is of help in ruling out some of the general considerations. Two atrioventricular valves were identified thereby eliminating

ing tricuspid atresia as a consideration. Only one great vessel was identified; consequently, pulmonary atresia is still strongly under consideration. The lack of continuity between a great vessel and a posterior atrioventricular valve is bothersome. No septum was seen and so one has to consider that the patient may have single ventricle with transposition of the great arteries and pulmonary atresia. This is a more complex abnormality than the tetralogy of Fallot but still has the functional abnormality, namely, obstruction to pulmonary blood flow from the heart and dependency of the patient on the patency of the ductus arteriosus. This dependency is supported by the clinical course of the child in that progressive hypoxemia and resultant metabolic acidosis occurred presumably secondary to progressive closure of the patent ductus arteriosus.

The complex anomalies that are seen in the asplenia syndrome have received much attention in the literature. The most common include pulmonary atresia, transposition of the great arteries and total anomalous pulmonary venous connection. In this particular case, however, the chest x-ray does not show discordance between the stomach bubble and cardiac apex, the tipoff to consideration of indeterminate situs and asplenia.

In summary, the case presents as an infant with persistent cyanosis. The cardiac examination suggested that the infant has a patent ductus arteriosus for his pulmonary blood flow. Laboratory tests support a diagnosis of pulmonary atresia in association with single ventricle and transposition of the great arteries.

DR EPSTEIN: Thank you, Dr Bessinger. I shall now describe the autopsy findings.

At autopsy, total situs inversus of both the thoracic and abdominal viscera was found. A single, normal appearing spleen was present in the right upper quadrant of the abdomen, as was the stomach. The essentials of the cardiac and vascular structural abnormalities are summarized in Fig 5.

The cardiac apex was directed to the right. The aorta arose anteriorly and to the left of the pulmonary trunk (Fig 6a). It ascended on the left and passed over the left bronchus. The descending aorta remained on the left side. The branches of the aortic arch from before backward were the innominate, left common carotid and left subclavian arteries. The previously performed right subclavian to right pulmonary artery anas-

tomosis was identified. The ductus arteriosus, now represented by a ligamentum arteriosum, ran between the aorta and left pulmonary artery.

The inferior vena cava was left-sided while the one superior vena cava was on the right.

The anatomic right atrium was on the left side of the heart. It received the inferior vena cava but not the superior vena cava. No coronary sinus was present. The left-sided anatomic right atrium also received the entire pulmonary venous return by way of a wide opening from an accessory chamber lying slightly posteriorly and superiorly (Fig 6b). A large inferoposterior atrial septal defect allowed free communication between the left-sided venous atrium and a smaller right-sided anatomic left atrium. The only venous connection with the right-sided arterial atrium was the solitary right-sided superior vena cava.

Below the inferoposterior atrial septal defect was a common atrioventricular valve of the complete type (Fig 6c). Among the leaflets of this valve were common anterior and posterior leaflets, each straddling a large deficiency of the ventricular septum. Through this free interventricular communication occurred. The configuration of the valvular tissue and the patterns of the tensor apparatus indicated that the left portion of the common atrioventricular valve was derived from the tricuspid component while the mitral component formed the right side of the common valve.

Of the two ventricles, the one that lay anterior and to the left was highly trabeculated and gave rise to an infundibulum and from the latter in turn arose the aorta (Fig 6c). The posterior ventricle, positioned on the right side, was smooth-walled and somewhat dilated. The outflow tract of the posterior ventricle was obstructed by accessory tissue which resembled atrioventricular valvular tissue (Fig 6d). This tissue arose from the anterior crest of the VSD and was directed posteriorly and superiorly, making an attachment to the anterolateral wall of the right-sided posterior ventricle.

The pulmonary valve arose from the right-sided posterior ventricle and was atretic. The pulmonary valvular tissue was in fibrous continuity with the mitral portion of the anterior leaflet of the common atrioventricular valve (Fig 6d). The pulmonary trunk measured only 2 to 3 mm in diameter at the annulus but gradually widened until it branched into relatively right and left pulmonary arteries.



Each lung was trilobed and on each side the broncho arterial relationships were those characteristic of the right lung (Fig 6a) All of the pulmonary veins drained into a common accessory atrium which in turn, drained through an unobstructed opening into the left sided anatomical right atrium

The coronary arteries arose from the aorta The left coronary artery entered the left sided AV sulcus without branching A short distance from the aorta the right sided coronary artery divided into anterior descending and circumflex branches

Dr Edwards would you please comment on this case?

DR EDWARDS: Several previously described anomalous complexes are brought together in this one case Included in these are (1) complete transposition in situs inversus\* (2) the inverse of the developmental complex of (a) termination of the left superior vena cava in the left atrium (b) absence of the coronary sinus and (c) a posteriorly lying atrial septal defect as described by Raghub and associates and (3) cor triatriatum terminating in the anatomical right atrium\*

In the developmental complex described by Raghub and associates, some subjects showed the basic complex coupled with persistent common atrioventricular canal as in this case In this combination the atrial septal defects of each of the two conditions coalesce yielding a large defect that includes all of the lowermost part of the atrial septum

In the syndrome of Raghub there are two superior venae cavae The case here presented shows a deviation in that the left sided right superior vena cava was absent

With regard to the association of pulmonary stenosis or atresia in complete transposition a number of anatomic states may cause obstruction to pulmonary flow Two were shown by this case each uncommonly seen in complete transposition These were pulmonary valvular atresia and subvalvular accessory endocardial tissue

In general the features of total situs inversus (with associated malformations) were displayed by this case but two exceptions are notable The first of these was the presence of a left aortic arch without retroesophageal segment This is not a surprising feature and may be viewed as the inverse of the relatively common right aortic arch without retroesophageal segment as seen in the

tetralogy of Fallot The other is the occurrence of bilateral right sidedness as far as the lung concerned This condition is classic for the aortic syndrome\* and its occurrence in association with an existing spleen adds unanswered questions about the association of splenic with organ laterality

The combined effects of the anomalies upon the circulation is of interest to consider

If one views this case as an example of cor transposition the fact that all of the pulmonary blood was carried into the left venous atrium was a favorable additional anomaly Similar is the fact that the solitary superior vena cava joined the atrial atrium In the presence of these 'venous crossings' the functional abnormality resides in the obstruction to pulmonary arterial flow in association with interventricular communication

**Final diagnoses** Situs inversus with cor transposition pulmonary atresia cor triatriatum leading to venous atrium persistent common atrioventricular canal and termination of superior vena cava in atrial atrium with a coronary sinus

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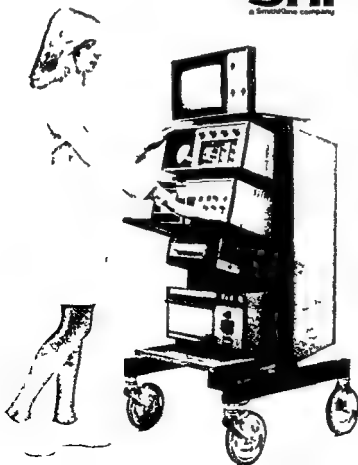
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*Joseph E Parrillo MD and Anthony S Fauci MD Bethesda Md*

Correlation of the location of coronary arterial spasm with the lead distribution of ST segment elevation during variant angina

*Rex N MacAlpin MD Los Angeles Calif*

Prognostic significance of an ST segment depression of patients with an acute coronary attack

*H Raunio V Ruusanen S Rehnberg V Jolinen M Helen and K Pyorala Kuopio Finland*

Low dose heparin in the prevention of deep vein thromboses in patients with acute myocardial infarction

*Aubrey Pitt MD FRACP Stanley T Anderson FRACI Peter C Haberberg FRACP and David S Rosengarten FRACS Melbourne Australia*

Captopril in severe treatment resistant hypertension

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The role of echocardiography in the selection of mitral valve prothesis

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Comparison of antiarrhythmic effects of oral prajmalium butyrate and intravenous lidocaine in acute myocardial infarction

*Wulf Dirk Busmann MD Sybille Schreiber and Martin Koltzsch MD Frankfurt W Germany*

The rhythm of the heart in active elderly subjects

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Recurrent angina after bypass surgery evaluation by early and late arteriography

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The effect of allopurinol on the degree of early myocardial ischemia

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Sudden death in cardiomyopathy role of bradycardia dependent repolarization changes

*Jack Buxton MD John W Watson MD James A Scott MD Valde S MD and David W Ohrt MD Little Rock Ark*

## Instrumental methods in the study of vascular disease

Jerrold S Lieberman MD

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Instrumental methods for assessing blood flow in the extremities facilitate the physiological approach to diseases of the peripheral circulation. An extensive clinical experience has developed using noninvasive techniques which are easily available to the clinician and basic determinations can be done at the bedside. The physician's history and physical examination remain the cornerstone of patient care but during the past decade laboratory testing has become an integral part of the clinical evaluation. In arterial occlusive disease these studies enable accurate diagnosis, precise localization, and quantification of the functional impairment. In venous thromboembolism they offer reliable screening tests and often an alternative to venography. In vasospastic disease they provide quantitative objective physiological evaluation. This review will describe the contribution of noninvasive testing and the vascular laboratory to the diagnosis and management of vascular diseases.

### Physiological considerations

In arterial occlusive disease (AOD) the major hemodynamic determinants of blood flow are the diameter of the stenosis and the velocity of blood flow (Fig 1A). Arterial stenoses and the terminal vascular bed are analogous to electrical resistances in series and stenosis becomes signifi-

cant when its resistance becomes comparable to that of the distal vascular bed. Reduction of the diameter of the arterial lumen has little effect until a large percentage of the cross-sectional area has been obliterated and a critical stenosis has been reached. Blood flow then falls off rapidly and progressively with a corresponding increase in the pressure drop across the stenosis (Fig 1B).

When velocity increases critical stenosis is reached at a lesser degree of narrowing and a previously non significant stenosis will produce hemodynamic abnormalities even though resting flow had been normal. Following exercise or a period of circulatory arrest by a tourniquet cuff blood flow in normal limbs will increase promptly up to 20 times the resting rate. However stenosis of the inflow artery as in AOD will delay the time of peak flow, reduce the absolute value of peak flow, and prolong the recovery time (Fig 2). When the systolic pressure is measured at the ankle AOD will reduce the pressure and prolong the recovery time. The initial drop is an index of main artery stenosis, and the increase in recovery time reflects the total flow deficit. The hemodynamic and pathophysiologic aspects of vascular diseases have been reviewed by Strandness and Sumner.

In clinical terms an atherosclerotic plaque will have little effect on blood flow until it has occluded a major portion of the arterial lumen. The inverse relationship between flow volume and pressure drop across a stenosis enables the physician to use the simple noninvasive indirect measurement of pressure to provide quantitative information on blood flow in the extremities and diagnostic maneuvers utilizing limb exercise or circulatory arrest will increase the sensitivity of

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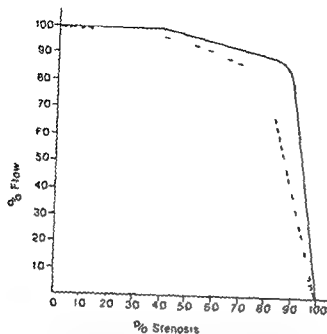


Fig 1A Arterial stenosis has little effect on blood flow until critical stenosis is reached it then causes a rapid and progressive decrease in blood flow. As flow velocity increases critical stenosis is reached at lesser degrees of stenosis and in this instance the resting flow rate at 80% stenosis (solid line) would show no significant abnormalities but if flow velocity were increased by exercise or reactive hyperemia as in the dashed and then dotted curves the reduction in flow would become significant.

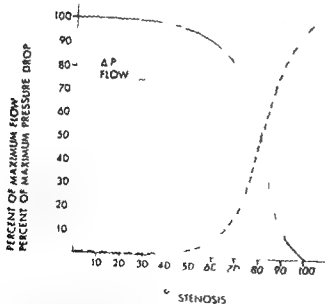


Fig 1B The pressure drop that occurs across the stenosis is inversely proportional to the resistance of the vessel and rises sharply as flow decreases. The initial measurement of systolic blood pressure at the site of stenosis in the vascular laboratory.

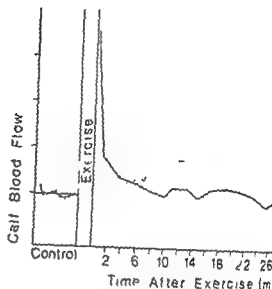


Fig 2 In a normal limb post exercise hyperemia (solid line) is characterized by prompt sharp peak flow and rapid return to control level. In a markedly ischemic limb (inter line) there is marked delay to peak time and prolonged recovery time.

the testing by increasing the velocity of blood flow.

The pathophysiology of arterial insufficiency demonstrated in intermittent claudication. In normal limb walking will cause a ten to twenty fold increase in calf blood flow but when there is proximal arterial stenosis the initial increase in flow will cause the stenosis to become critical. The increased pressure drop will decrease distal arterial pressure until intra-arterial pressure within the calf muscle falls below the surrounding tissue pressure. At this time flow through the muscle bed will fall dramatically or cease. A characteristic ischemic pain will appear. When the patient halts muscle contractions cease and in the recovery phase pain continues until the metabolic debt has been repaid. During the recovery phase the hyperemic flow through the calf muscle creates a shunt which steals from the ankle and increases the drop in ankle blood pressure. Since walking distance is related to the stenosis of the large arteries and also to the workload it is predictably influenced by the speed of walking or by grades.

On physical examination the normal nutritional state of the feet will attest to the normal resting blood flow. In early claudication and advanced disease trophic skin changes show that stenosis is critical even at resting flow rates.

Pallor in elevation is indicative of large artery involvement with reduced pressure while dependent rubor indicates dilation of the capillary bed in response to ischemia and reduction in total blood flow. In patients with early stenosis or segmental occlusion with good collaterals, the pulse may be palpable at rest but disappear with exercise.

The venous bed is easily distensible and flow is low and not pulsatile. As a result physical examination is notoriously unreliable in the estimation of venous flow and in the recognition of thrombophlebitis, which is a venous occlusive disease. In the hand skin color provides an enjoyable and direct demonstration of blood flow. In the Allen test, the rate of flow into the hand is directly visualized when the physician releases his pressure at the patient's wrist. Hang ups indicate occlusion of the smaller arteries and the duration of the hyperemic flush gives a measurable recovery time.

### Instrumentation

**Plethysmography** is the measurement of changes in the volume of an organ or limb and is the reference standard for the measure of blood flow in the extremities. The original technique was cumbersome and time consuming but newer pneumatic plethysmographs utilize simple cuffs for the calf studies and plastic cups for toes and fingers. Electronic transducers provide an analog readout.

Indirect methods have further enhanced the flexibility and availability of the plethysmographic technique. The mercury strain gauge (MSG) is a slender elastic tube filled with mercury which encircles the limb or digit. Changes in the circumference and volume of the limb segment enclosed by the gauge will generate an analog signal which is linearly related to the volume changes. Simple black boxes are commercially available in which a closed loop gauge is slipped over the tip of a finger or a toe. These units which are usually not calibrated attach directly to the office electrocardiogram to give pulse wave traces at the bedside. Calibration can be done off the limb with a micrometer.

In impedance plethysmography (IMP) two electrodes are applied directly to the limb and when a high frequency low current signal is passed between them the changes in blood vol-

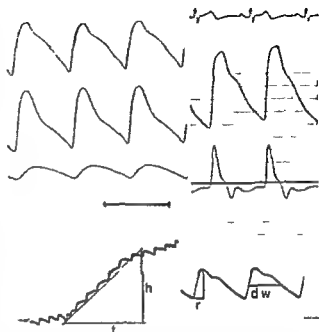


Fig 3 Plethysmography. Upper left Simultaneous, standardized digital pulse wave forms as recorded with a pneumatic plethysmograph (Windsor) from above a normal finger, a normal toe and a toe distal to a low grade femoral popliteal occlusion. Time marker is 1 second. Upper right A normal toe pulsation as recorded with mercury strain gauge. The first derivative is recorded below and resembles the velocity curve or the Doppler signal. Lower left Finger blood flow by venous occlusion plethysmography. With calibration  $h/t$  represents the blood flow/unit of time/volume of tissue. Lower right Rise time ( $r$ ) width at half amplitude ( $dw$ ) when expressed as percentage of cycle length are easily obtained and enable simple quantification.

ume between the electrodes will generate voltage changes proportional to blood flow. When four electrodes are used this method can be calibrated in accurate percentage changes but absolute values cannot be obtained. IMP is widely used for venous outflow studies.

Any of the plethysmographic methods can be used to determine systolic blood pressure (SBP) to record digital pulse wave forms or to evaluate arterial or venous flow by venous occlusion (Fig 3). For SBP the plethysmograph is used as a pulse detector corresponding to the stethoscope in the auscultatory technique. It will give accurate measure of the systolic pressure at the site of the cuff regardless of where the distal sensor is positioned. However the diastolic pressure cannot be obtained.

Digital pulse wave forms lend themselves easily

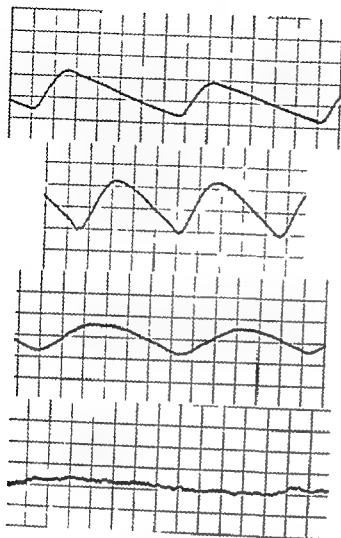


Fig 4 Line pulsation with the mercury strain gauge. The top trace is normal as the dicrotic notch does not lose its position in normal pulsations. With progressive arterial insufficiency the type of the ascending limb is delayed at the peak time is delayed and the downstroke becomes irregular. In the third trace the umbrella wave in the third pulse the arterial flow is no longer palpable. The wave is a reflection of the flow.

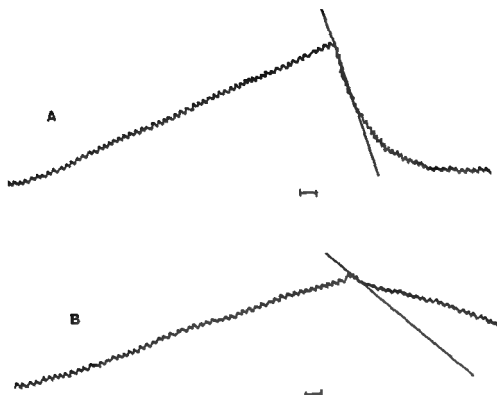
to analyze in pulse form. For quantitation the simple time intervals of rise time and pulse width at half amplitude have been described (Fig 3). With the calibrated instruments absolute pulse dimensions can be obtained. The plethysmographic signal is easily differentiated electronically and the first derivative resembles the velocity wave form in the pulse. Burkh has described sophisticated method for waveform analysis.

Quantitative measurement of arterial blood flow is accomplished by venous occlusion plethysmography with pneumatic cuff strain gauge techniques. A cuff is applied proximally to the part that is to be studied and after calibration and base-

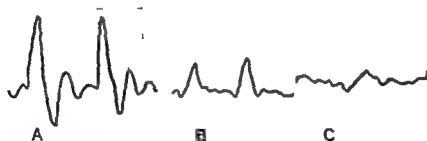
line stabilization the cuff is rapidly inflated to subdiastolic pressure usually 40 to 60 mmHg. Initially only venous outflow is blocked and arterial blood will distend the vascular bed. When the venous pressure reaches occluding pressure the slope of this volume tracing represents arterial blood flow (Fig 3). For acute studies amplitude of the digital pulse wave is a function of blood flow to the digit and is an accurate index of changes in blood flow. Measurement cannot be calibrated and percentage changes can be obtained. Normal pulse wave forms have a rapid systolic upstroke, a sharp peak early in the cycle and a delayed downstroke with upward concavity. A small notch is usually present in the fingers but not in the toes. Distal to a stenosis the plethysmographic curve loses its characteristic shape and undergoes progressive loss of amplitude and deteriorates from an umbrella shape to a straight line (Fig 4).

In venous studies peak venous outflow is measured by positioning the plethysmograph on the calf. A collecting cuff above the knee is inflated to a venous collecting pressure and rapidly deflated while the volume change is recorded (Fig 5).

The Doppler Flowmeter (DFM) determines blood velocity by a noninvasive transcutaneous method. Two piezoelectric crystals are mounted in a hand held probe which is placed over an artery or vein and contact is made through acoustic gel. The transmitting crystal is connected to emit an ultrasonic beam at a frequency between 2 and 10 MHz and when a small percentage of the beam is reflected back by the moving cells within the vessel the frequency of the signal is altered in accordance with the Doppler shift. The reflected sound wave generates a small electrical signal in the receiving crystal. The emitted and received signals are compared electronically and the instrument generates an audible signal whose frequency is proportional to flow velocity—a higher pitch representing a greater velocity. With DFM observation of the audio signal represents a subjective form of waveform analysis and the nonarterial signal can be recognized by the triphasic configuration. Distal to a stenosis or occlusion the signal will be low pitched and monophasic. These signals can also be recorded graphically (Fig 6). Quantitative velocity re-



**Fig 5** Impedance plethysmography for venous outflow in a normal limb (A) and with deep vein thrombosis (B). The maximum venous outflow (MVO) is drawn by inspection and is reduced in the lower tracing.



**Fig 6** Arterial signals with the Doppler flow meter analog recording. A The normal signal is made triphasic by the reverse flow in early diastole with subsequent forward flow. B With early stenosis peak flow is lower and there is loss of diastolic reverse flow. C With severe stenosis the rate of flow is markedly reduced, the pitch is lower and the signal is highly damped.

measurements and the analysis of slopes, areas and time intervals have been used to generate sophisticated flow indices including the pulsatility index, damping factor, transit time and turbulence factor. Spectral analysis requires further instrumentation and will display the distribution of multiple velocities in real time.

Because of its availability and the ease with

which it can be used, DFM has become a first line instrument widely used in clinical practice. The audio signal provides a simple, accurate pulse detector for the determination of segmental systolic blood pressures and can be interpreted by auscultation. In daily practice, the instrument may become part of the physician's routine vascular examination, much like the ophthalmoscope.



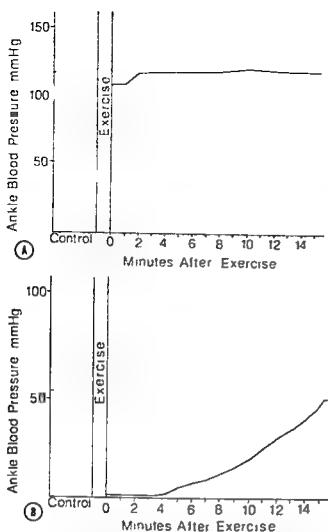


Fig 7 Ankle blood pressure response to treadmill exercise. *A* There is no significant change in AP in the normal limb after 5 minutes of treadmill exercise. *B* With moderate arterial insufficiency, the control blood pressure is lower than the brachial, AP falls after exercise, and recovery is delayed.

scope or stethoscope. As a detector of venous blood flow, the instrument enables bedside elucidation of venous hemodynamics for the detection of deep vein thrombosis. Pocket size and small portable instruments are available commercially. The smaller audio units and the less sophisticated analog devices determine the presence and relative velocity of flow but not the direction. They are adequate for most clinical studies and the directional information is more likely to be required for quantitative studies or physiological investigation. DFM is extremely sensitive and signals may be obtained from small arteries. Detection of a flow signal is not necessarily equivalent to palpation of an arterial pulse on physical examination.

High technology imaging techniques use intermittent ultrasound pulses rather than continuous waves. They enable the display of sectional areas in real time and Doppler profiles at specific sites within the vessel. Noninvasive techniques. Radioisotope studies use washout techniques to measure flow in skin and muscle. They have not been used extensively in the clinical vascular laboratory.

### Arterial occlusive disease

The laboratory evaluation of AOD utilizes noninvasive indirect determination of blood flow in association with the relationships shown in Fig 2. The primary measurement is the ankle-arm pressure and additional information is obtained from systolic pressures at other levels, the response to exercise or reactive hyperemia, and waveform analysis.<sup>17-21</sup>

For ankle systolic blood pressure (AP), the probe is applied to the lower leg just above the medial malleolus. If DFM is used, the probe is held over the posterior tibial or dorsalis pedis artery, or the probe is held over the artery as heard as with a stethoscope. In plethysmography, the sensor is applied to a toe. The appearance of pulsatile flow is observed on the strip chart recorder. In normal subjects, the ankle AP will be about 15 mm Hg higher than the brachial. A gradient is said to exist when the ankle pressure falls below the brachial. It indicates hemodynamically significant arterial stenosis or occlusion and its magnitude corresponds roughly to the degree of arterial insufficiency. The gradient is often expressed as the perfusion index (PI) by dividing AP by the brachial pressure. It will be unity or greater in normal limbs and a PI less than 1 is indicative of arterial insufficiency. As PI decreases, it indicates greater reduction in blood flow. With a single stenosis, PI will be between 0.5 and 1, but multiple stenoses will impose greater restriction on arterial flow and the PI will be below 0.5.

Segmental systolic blood pressures provide further information. Measurements may be taken on the thigh, above and below the knee, at the ankle, and on individual toes. These measurements enable accurate localization of lesions and evaluation of their hemodynamic significance. Even with a special cuff, the pressure may be artifactually elevated by as much as 30 mm Hg, but other pressures approximating

temic in the normal limb and a pressure drop of 30 mm between two successive stations indicates a hemodynamically significant lesion.

For wave form analysis quantitative plethysmographic tracings can be obtained at the same levels as the systolic blood pressures and have been utilized in the Pulse Volume Recorder (PVR). Doppler wave form analysis provides corresponding information and has been utilized in the evaluation of aortoiliac disease.

As examples of clinical application a PI of less than 55 suggests that an ischemic ulcer is unlikely to heal without reconstructive surgery and when SBP toe falls below 30 mm there is high likelihood that gangrene will appear. In a study of below knee amputations Barnes and colleagues found that when SBP below knee was greater than 70 mm Hg operative sites healed well but that when the pressure was below 50 mm Hg there was a significant risk of non healing.

Ankle pressure gradients may fail to detect early stenosis or may be equivocal. Exercise testing is helpful in this instance and will also provide better evaluation of total limb flow. Exercise testing has been performed largely on the treadmill with Doppler determinations of AP. The procedure is not standardized for speed and grade but the exercise is usually continued for five minutes unless claudication appears sooner. AP is determined immediately after the exercise and at one minute intervals until the pressure returns to the control level to determine the initial pressure drop and the recovery time. A pedal ergograph may also be utilized and Carter has used simple ankle flexion against the examiner's hand. In our laboratory we have found 15 toe stands in 30 seconds to be a satisfactory exercise load and Hummel and associates reports that 30 toe stands are equivalent to the usual exercise test. With these work loads normal subjects will maintain AP at control levels or show a brief drop of less than 15 mm Hg. With arterial insufficiency the pressure will fall at least 20 mm or 20% from baseline and the recovery time may be from 4 to over 15 minutes. The initial drop reflects the degree of occlusion of the main arteries while the recovery time measures total limb flow including collaterals. The patterns of response can differentiate single from multiple occlusions (Fig 7).

Exercise tests require space equipment and the patient's cooperation. They are time consuming when arterial insufficiency is severe and the

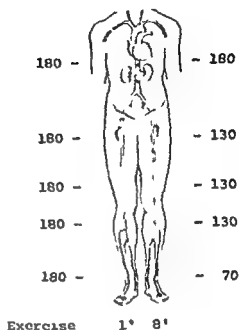


Fig 8 A vascular laboratory study. The right leg is normal. On the left the segmental systolic blood pressures indicate stenosis or occlusion of the left iliac artery and of the calf vessels distal to the popliteal. The digital wave form recovery time and pressure index of 0.40 indicate moderate arterial insufficiency.

workload makes it advisable that resuscitation procedures be available. For these reasons the exercise load may be replaced by a period of circulatory arrest thus measuring post occlusive reactive hyperemia (PORH). A thigh cuff is inflated to an occluding pressure for 3 to 5 minutes and on its release reactive hyperemia will occur with an accelerated time scale. Hummel and co workers' reported good correlation between PORH and treadmill exercise with a reduction in observation times from 20 minutes to 2 minutes. AP was recorded at 15 second intervals. Fronck and associates' occlude the arterial inflow for 4 minutes and measure PORH by observing increased velocity at the femoral artery with a Doppler probe. They use the MSG simultaneously to follow the disappearance and subsequent return of pulsation in the toe.

In our own laboratory the basic arterial study

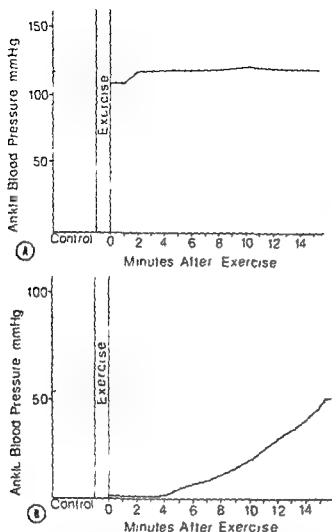


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apetitive compression of the foot or lower calf and readout by a six channel strip chart recorder gives information on the propagation of respiratory waves through the limb and the volume responses to compression. This instrument enables a sophisticated semiautomated examination of the venous system but requires formal training for both the technician and the interpreting physician. An accuracy of greater than 95% has been reported but confirmation by other laboratories has not yet been established.

In the *radio fibrinogen uptake test* I labeled fibrinogen is administered intravenously and the legs are then scanned at intervals of one or more days with a hand held scintillation detector and rate meter. When the count at one location remains significantly elevated for 24 hours the 'hot spot' indicates that labeled fibrinogen is being incorporated into newly forming thrombus usually indicating the initial formation of thrombus within the venous arcades of the soleus muscle and the smaller veins of the calf. Only half of these patients will have clinical signs of phlebitis and of all patients with abnormal uptake approximately 20% will extend into the popliteal femoral and iliac veins. The test is limited by inability to detect thrombi in the pelvis or groin and a high false positive rate in the presence of trauma infection local surgery or bleeding. It lacks precise localization of the extent of the thrombus and may not become positive until 72 hours after the isotope has been injected. The test has been used extensively for prospective screening and provided the technological support for the recent studies of post surgical deep vein thrombosis and prophylaxis with low dose heparin.

When used for clinical diagnosis the test is usually combined with a hemodynamic method as the false positive rate may reach 30%. Because it indicates the active incorporation of fibrinogen into the clot it has been used to evaluate the recurrence of deep vein thrombosis in patients with post phlebotic edema who develop fresh symptoms but there are divergent reports on its reliability.

#### Clinical application

The clinical diagnosis of DVT has an accuracy of approximately 50% and it is therefore advisable to confirm the diagnosis by at least one method before committing the patient to a full course of anticoagulation. The initial testing may

be done by Doppler ultrasound or by plethysmography according to the experience and facilities of the physician or hospital. Either method is suitable and when the two are combined correlation with the venogram may reach 95%. Fibrinogen uptake testing is sometimes combined with impedance plethysmography. The role of phleboreography has not yet been established.

When the vascular tests are abnormal and the totality of history physical examination and test results is sufficient in the physician's judgment to support the diagnosis of DVT anticoagulants may be given. When the tests are equivocal or if another etiology such as extraluminal compression of the vein by pelvic tumor is suspected then the venogram becomes necessary. When the tests are normal but clinical suspicion is high there may remain the possibility that thrombi are present in the deep femoral or calf veins or that non occlusive thrombi are present in the popliteal or more proximal veins. This problem should also be resolved by contrast venography. When there are relative contraindications to anticoagulation and the venogram shows clots confined to smaller veins of the calf the physician may elect to withhold anticoagulants and to monitor the patient with periodic noninvasive testing. If subsequent tests show extension into the proximal veins the then documented risk of pulmonary embolism can be weighed against the hazards of anticoagulation for the individual patient.

In the evaluation of other venous disorders ultrasound and plethysmographic studies are effective in differentiating lymphedema from post phlebotic edema and from deep vein thrombosis. The role of hemodynamic studies in the management of varicose veins has not yet been determined.

All laboratory methods demand ongoing quality control. For deep vein thrombosis this means correlation of the instrumental results with venography clinical outcome and the findings at surgery and postmortem. This is particularly true of Doppler ultrasound studies since the availability of the instrument may tempt untrained personnel to assign an unwarranted accuracy to their results.

#### Arm and hand

Occlusive disease of the large arteries of the arm is easily detected by segmental systolic blood pressures with Doppler or plethysmographic pulse detection. An exercise test can be performed

## Clinical pharmacology of the new beta-adrenergic blocking drugs Part 12 Beta-adrenoceptor blockade in myocardial infarction the continuing controversy

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Beta adrenoceptor blocking drugs have been shown to be safe and effective in the treatment of patients who have hypertension, angina pectoris, hypertrophic cardiomyopathy, thyrotoxicosis, glaucoma and migraine headaches.<sup>1</sup> However the role of these agents in the treatment and prevention of myocardial infarction is controversial due to a lack of adequately controlled clinical trials.

These agents are employed with a view toward improving the quality as well as the quantity of life even though there is no adequate clinical data to prove the latter. The theoretical considerations and clinical experience in the use of beta adrenoceptor blocking drugs during the acute phase of myocardial infarction and for the primary and secondary prevention of acute myocardial infarction and sudden death are assessed in this article.

### Primary prevention (myocardial infarction and sudden death)

While beta adrenoceptor blockade does not directly affect the progress of coronary atheroma it does reduce myocardial oxygen requirements. This in turn enables the cardiac muscle to tolerate for a while what would otherwise be an

inadequate supply of oxygen. The reduction of oxygen requirements is due to a decreased heart rate and reduction in myocardial contractility. Beta blockade may improve distribution of flow in the ischemic myocardium<sup>2</sup> as well as improve the utilization of myocardial substrate.<sup>3</sup> These drugs are known to inhibit platelet aggregation and to be potent antiarrhythmic agents.<sup>4</sup>

In patients with angina pectoris these agents have been useful in reducing pain and improving exercise tolerance. An adequate degree of beta adrenoceptor blockade affords marked relief from pain in 80% of cases. This success rate can be improved by selecting the best tolerated beta blocker in combination with nitrates. Thus the quality of life can be improved in patients with angina pectoris.

A major unresolved question in clinical medicine is whether the beta adrenoceptor blockers can influence the natural course of stable angina pectoris by prolonging the patient's life expectancy and by reducing the risk of infarction. There are multiple subgroups of patients with angina pectoris defined by differences in symptomatology (stable or unstable), coronary anatomy, left ventricular function and stress test results. These multiple variables make a proper study design almost untenable. The few pooled data studies that have been completed have not demonstrated any marked reduction in the annual mortality rate of patients with stable angina pectoris when compared to results of large epidemiologic studies.<sup>5-7</sup> While patients are treated with beta adrenoceptor blockers to improve the

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quality and quantity of life only the quality of life has proven to be enhanced

Nevertheless beta blockade is the treatment of choice for the symptomatic relief of angina pectoris. However as in the case with lipid lowering and platelet inhibiting agents only theoretical considerations suggest employing beta adrenoceptor blocking drugs as primary prophylactic treatment against myocardial infarction and sudden death. Prospective studies with high risk individuals are necessary to determine whether primary preventive treatment will indeed prolong life and/or prevent sudden death. In lieu of definitive proof of efficacy primary prophylactic treatment is cost ineffective.

While no definitive evidence exists for the primary prophylactic benefits of beta adrenoceptor blocking drugs preliminary data suggest that these drugs may be useful in the secondary prevention of reinfarction and sudden death<sup>1</sup>.

#### Beta adrenoceptor blocker therapy in acute myocardial infarction

In patients with acute myocardial infarction the presence of severe pain, tissue injury and circulatory disturbances are important physiological stresses which trigger an increased sympathoadrenal discharge. This observation is based on evidence derived from several studies of urinary free catecholamine excretion<sup>1</sup> and measurements of plasma catecholamine levels during the early stages of myocardial infarction<sup>2</sup>.

An increase in circulating catecholamine levels following myocardial infarction may have an important supportive role in the maintenance of the contractile performance of ischemic areas of the myocardium as well as enhancing the residual ion ischemic areas. However there are two important and potentially deleterious consequences of an increase in sympathetic nervous activity:

1. Increased sympathoadrenal discharge may be the cause of serious cardiac arrhythmias after myocardial infarction.

2. The positive inotropic and chronotropic effects of catecholamines lead to an increase in total cardiac work and myocardial oxygen consumption. This may be critical particularly in areas of ischemia at the border of an infarct in which increased oxygen demands may extend areas of necrosis. Isoproterenol has been shown to impair both performance and metabolism of an

ischemic myocardium which suggests that enhanced neuroadrenergic activity may be harmful.

Beta adrenoceptor blocking drugs have logically been considered for use in patients with acute myocardial infarction to prevent the undesirable consequences of increased sympathoadrenal discharge. These agents favorably influence some of the determinants of myocardial oxygen consumption. On the other hand beta adrenoceptor blockade can have dangerous consequences in some cases of fresh infarction. Impulse formation may be greatly impaired and conduction diminished to a degree that causes cardiac arrest. Furthermore exacerbation of congestive heart failure due to the elimination of the positive inotropic effect of catecholamines has been a known sequela of beta blockade.

**Antiarrhythmic effects.** The value of beta adrenoceptor blockade in patients with dysrhythmias has been established. However the antiarrhythmic efficacy of beta blockade in acute myocardial infarction has not been well documented.

The arrhythmogenic actions of catecholamines have been recognized for over 70 years. Recently it has been found that removal of sympathetic influences to the heart by whatever means will lead to a reduction in the incidence of arrhythmias following experimental coronary occlusion in animals. Furthermore the occurrence of ventricular arrhythmias in experimental infarction was found to be associated with increased levels of catecholamines<sup>3</sup>.

The exposure of ischemic tissue to high levels of catecholamines favors the appearance of multiple reentry pathways and the development of ventricular tachyarrhythmias and ventricular fibrillation<sup>4,5</sup>. These experimental data suggest that beta blockade would be particularly effective in preventing or aborting arrhythmias in acute myocardial infarction.

Experimental studies in dogs with myocardial infarction revealed that pretreatment with beta adrenoceptor blockers prevented or reduced the incidence of malignant ventricular tachyarrhythmias.

Randomized controlled trials comparing propranolol and alprenolol to placebo in patients with acute myocardial infarction have not revealed differences in the incidence of mortality or morbidity (heart failure or arrhythmia).

These studies have been criticized for failing to measure plasma drug levels and for using a fixed dose regimen rather than titrating the drug to the patient's requirements.

Lemberg and colleagues<sup>44</sup> reported the first major experience using beta blockers in the elective management of arrhythmias after acute myocardial infarction. These investigators reported favorably on the elective use of propranolol in 34 patients who had 43 episodes of tachyarrhythmia following an acute myocardial infarction complicated by mild to moderate heart failure. The dosage of propranolol employed in these studies was 0.5 to 0.7 mg intravenously given at 2 minute intervals until sinus rhythm returned or the ventricular rate slowed down to 80 beats/minute. The arrhythmias included examples of atrial fibrillation, atrial flutter, supraventricular tachycardia, and ventricular tachycardia, all with ventricular rates over 140 beats/minute. A majority of patients responded to a total intravenous dose of less than 5 mg of propranolol.

Lemberg and co-workers<sup>45</sup> also investigated the use of alpranolol in acute cardiac arrhythmias in patients with infarction and found the drug to be as effective as propranolol in both supraventricular and ventricular arrhythmias. The average intravenous dose was 9.5 mg (range 2 to 20 mg). Comparable experiences with oxprenolol and pindolol have been reported.

Beta adrenoceptor blockers have been proved efficacious in the treatment of many patients with atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, junctional tachycardia, and lidocaine-resistant ventricular arrhythmias. These drugs may be used adjunctively with other antiarrhythmic agents as well as in dc electrocardioversion. Overall, the beta adrenoceptor blocking drugs are more effective in paroxysmal supraventricular tachyarrhythmias than they are for ventricular rhythm disturbances.

The therapeutic efficacy of beta adrenoceptor blockade as an antiarrhythmic intervention is well accepted. However, potential side effects must be considered when employing beta blocking drugs. These agents, in case or potentiate congestive heart failure, hypotension, atrioventricular conduction delay, and airway obstruction.

It is for these reasons that the routine prophylactic administration of these drugs to all patients with acute myocardial infarction is not justified without hemodynamic monitoring. When using beta blockers as antiarrhythmic

agents in acute myocardial infarction the deleterious effects of tachyarrhythmias in hemodynamic terms and the benefits of reversion to normal rhythm or slowing of the rapid ventricular rate must be balanced against the possible cardiovascular depression produced by the drugs themselves.

Whether or not beta adrenoceptor blockers, drugs with intrinsic sympathomimetic activity (pindolol, acebutolol, oxprenolol) will provide superior antiarrhythmic alternatives to propranolol has not been proven in clinical trials.

**Reduction or containment of myocardial infarction.** Beta adrenoceptor blockers would be used extensively in acute myocardial infarction were it not for their negative inotropic effect. Beta adrenergic activity is important for diseased hearts.<sup>46,47</sup>

The negative inotropism of these drugs relative to antiadrenergic effects rather than membrane depressing properties.<sup>48,49</sup> The negative inotropic effect of beta adrenergic blockade is not clinically important without evidence of left ventricular dysfunction.<sup>50</sup>

Early clinical studies (prior to 1970) in acute myocardial infarction where oral propranolol was employed as a prophylactic agent revealed no clinical benefit.<sup>51</sup> After these preliminary results, beta adrenoceptor blockers were not used in myocardial infarction until the 1970's. Their use was suggested when investigators recognized that the development of irreversible left ventricular pump failure was related to the area of damaged myocardium, emphasizing a need to preserve the ischemic myocardium. It is now well established that myocardial infarction is not an all or none phenomenon. It has been shown that there is an ischemic region around the infarcted area that may not necrose until several hours or days have elapsed.<sup>52</sup> It has been demonstrated that reduction of myocardial oxygen requirements will decrease the final size of an infarct and an increase in oxygen requirements will increase the infarct.<sup>53,54</sup> In dogs with experimental occlusion of a coronary artery, propranolol will reverse the epicardial ST segment elevation of the electrocardiogram, changes which are said to reflect a reduction in the predicted size of the myocardial infarct.<sup>55</sup> Of interest is the fact that exogenous catecholamines have been found to have the reverse effect.

In man, Pelides and colleagues<sup>56</sup> have shown that practolol given within 72 hours of an acute

reduced the precordial ST segment elevation. These findings were amplified by Mueller and co-workers<sup>1</sup> who demonstrated a reduction of myocardial hypoxia as estimated by increased lactate uptake in patients (Class I and II New York Heart Association Classification) after intravenous propranolol was administered within the first 12 hours of infarction. In the study by Mueller and associates, there was no deterioration in clinical left ventricular function. Reductions in cardiac contractility, cardiac index, and myocardial oxygen consumption in patients were associated with improved myocardial metabolism and bioenergetics. Despite these favorable hemodynamic and metabolic findings, the investigators could not demonstrate an absolute decrease in infarct size or an increase in ultimate survival. *The difficulties in assessing a reduction in predicted myocardial infarction size are due to problems with the measuring modalities.*

Gold and co-workers<sup>2</sup> recently demonstrated a reduction in ischemic injury (defined by reduction of ST segment elevation) on the ECG when intravenous propranolol was given during acute myocardial infarction. These effects were less marked however in patients with total coronary occlusions. These findings suggest that (1) propranolol may be more effective in subendocardial wall infarction where flow is not completely compromised and in this case ischemia may be a more important component than necrosis; (2) propranolol may be less effective in transmural myocardial infarction with more complete cessation of effective flow and where necrosis may greatly overshadow reversible ischemia. Nevertheless, these data suggest that a reduction in myocardial oxygen demand might arrest the stepwise progression of myocardial necrosis.

The results of a study by Cairns and co-workers<sup>3</sup> demonstrated that propranolol administered an average of ~6 hours after acute myocardial infarction in 20 patients appeared to delay the evolution of infarction. In a randomized double-blind clinical trial by Pitt and colleagues<sup>4</sup> propranolol was shown to reduce infarct extension.

The benefit to-risk ratio must be calculated for each patient prior to the use of beta adrenoceptor blockade in acute myocardial infarction. There are inherent problems with this therapy that must be considered.

1. Beta adrenoceptor blockers may increase left ventricular volume and end diastolic pressure

by their negative inotropic effects especially in severely damaged hearts. "By this mechanism they may increase the oxygen demands of ischemic myocardial tissue. At the same time increased left ventricular end-diastolic pressure can limit an already compromised subendocardial blood flow. These risk factors could easily offset the beneficial reduction in heart rate and blood pressure with beta adrenoceptor blockade."

2. Since patients have varying degrees of sympathetic tone, there is no established beta adrenoceptor blocking dose with any agent. "One patient might require a dose four times that of another patient to achieve the same beta blocking effect. The drug should also be given intravenously in acute myocardial infarction to achieve its immediate effects and this might precipitate sudden bradyarrhythmias or conduction abnormalities."

3. Despite the adverse effects of isoproterenol recently defined in experimental animals with myocardial infarction, heightened sympathetic tone may not be deleterious for all patients. Some patients with a considerable amount of frank necrosis and little ongoing ischemia may need their sympathetic tone to preserve pump function. Beta adrenoceptor blockade could actually worsen cardiac failure in these patients.<sup>5</sup>

The widespread administration of beta adrenoceptor blocking agents to patients with myocardial infarction is not indicated unless hemodynamic monitoring is available to assess the benefit to-risk ratio in any given patient. Where ischemia rather than necrosis is the cause of the pathological problem, beta adrenoceptor blockade is recommended especially in those patients with preinfarction states ("intermediate syndrome"). By decreasing heart rate, blood pressure, and contractility, beta adrenoceptor blockade reduces ischemia and relieves pain. Left ventricular function, which may be transiently depressed in acute ischemia, generally improves as the ischemia is lessened.<sup>6,7</sup> Once the situation is stabilized medically, more definitive measures including coronary angiography and when appropriate coronary artery bypass surgery may be considered.

Excluding patient contraindications, the recommended dose of propranolol for treatment of acute and prolonged myocardial ischemia is 0.05 to 0.10 mg/kg (lean body weight) administered intravenously at a rate of 1 mg/minute.<sup>8</sup>

It should be followed by an oral dose



designed to achieve adequate beta adrenoceptor blockade

The potentially protective properties of propranolol in acute myocardial ischemia in the absence of infarction have been reported by several groups. In a randomized double blind study of 68 patients with unstable angina the propranolol treated patients experienced fewer coronary events than placebo treated patients. In patients admitted to a coronary care unit because of prolonged ischemic chest pain a myocardial infarction developed less frequently under long term treatment with beta adrenoceptor blocking drugs. 30 to 90 patients experienced infarction in contrast to 62 of 90 patients who did not receive the drug.

Beta adrenoceptor blocking drugs are indicated when angina pectoris develops after acute myocardial infarction and in a subgroup of patients with myocardial infarction associated with a hyperkinetic circulatory response (i.e. hypertension, tachycardia) without evidence of left ventricular dysfunction.

The results of experimental and clinical research suggest that beta adrenoceptor blockade can play an important role in the treatment of acute myocardial infarction. This blockade decreases cardiac work and improves perfusion and metabolism of ischemic myocardium. The effectiveness of beta adrenoceptor blocking agents primarily depends upon the functional state of the heart. The more left ventricular function is determined by the mechanical and contractile properties of ischemic areas the more likely beta adrenoceptor blockade will improve oxygenation of the jeopardized myocardium. However a deleterious effect can be anticipated when the ventricular performance is primarily determined by frank myocardial necrosis. With careful evaluation of the benefits to risk potential in individual patients, beta adrenoceptor blockade can be a useful therapeutic intervention for protecting the ischemic myocardium in acute myocardial infarction.

#### Secondary prevention of myocardial infarction and sudden death

There is currently a 10% mortality rate one year following a myocardial infarction and this mortality occurs within one hour of the onset of symptoms in approximately half of these cases. A therapeutic goal is to decrease the

mortality rate in this group of patients who are at high risk of sudden death. Ventricular tachyarrhythmias are now considered the most important cause of sudden death in patients who are less than 70 years old.

A significant reduction in mortality by continuous treatment with procainamide, quinidine, phenytoin as well as other new antiarrhythmic agents after myocardial infarction has not been demonstrated in controlled clinical trials. Short term trials using propranolol following acute myocardial infarction have shown conflicting results. Snow in 1965<sup>11</sup> first reported a substantial reduction of mortality in patients with myocardial infarction who had received propranolol. He treated 52 patients with 60 mg propranolol daily for 21 days and compared this to 55 control subjects. The results while impressive were not conclusive because it was an open label study without a double blind control group. Several randomized double blind studies have then initiated. These included about 250 patients with acute myocardial infarction who received an average of 40 to 80 mg of oral propranolol daily. These controlled studies failed to confirm the findings of Snow.<sup>12</sup> There were no significant differences in mortality, shock, heart failure, hypotension or arrhythmias between the treated and the untreated patients.

The first long term study using a beta adrenoceptor blocker also failed to demonstrate decreased mortality rate. In this double blind randomized study by Reynolds and White<sup>13</sup> (Table I) 78 patients were given 100 mg alprenolol or placebo four times daily for six weeks following the time of admission to a hospital coronary care unit. This trial may have been too short a duration and may have involved too few patients to show a difference.

Two major clinical trials from Sweden using alprenolol in patients with myocardial infarction have since been completed.<sup>14,15</sup> Alprenolol was chosen as the beta adrenoceptor blocker for these studies owing to its moderate intrinsic sympathomimetic action and consequent theoretically reduced risk of causing sinus bradycardia. The objectives of these studies were to investigate whether the incidence of recurrence of infarction, sudden death and total mortality was influenced in patients treated with a beta adrenoceptor blocker.

In the study by Wilhelmsson and colleagues

Table 1 Reported efficacy of long term beta adrenoceptor blockade in preventing reinfarction and sudden death

Study	Patients (no)	Duration of Study	Regimen	Non fatal reinfarction	Sudden death	Total mortality
Reynold and Whitlock	78	1 year	Alprenolol (39)	4 (NS)	2 (NS)	3 (NS)
			Placebo (39)	4	1	3
Wilhelmsson et al	230	2 years	Alprenolol (114)	16 (NS)	3 (p < 0.05)	7 (NS)
			Placebo (116)	18	11	14
Ahlmark et al	162	2 years	Alprenolol (69)	4 (p < 0.05)	1 (p < 0.05)	5 (NS)
			No therapy (93)	15	9	11
International Multicentre Study	3038	Up to 3 years (mean in 14 months)	Practolol (1514)	69 (p < 0.10)	30 (p < 0.02)	47 (p < 0.02)
			Placebo (1524)	89	52	73

NS = not statistically significant

Study had to be terminated because of no significant effects of practolol

Reduction in total cardiac mortality rate was only significant for patients with previous anterior wall myocardial infarction

(Table 1) patients who had a myocardial infarction were less prone to sudden death if treated with a beta blocking drug. In this small but well controlled study, 230 patients who had sustained a myocardial infarction were grouped into four separate risk strata which were determined by the degree of previous myocardial damage. Within each stratum alprenolol (400 mg daily) or placebo was randomly assigned to patients over two years. Within each stratum the incidence of non fatal reinfarction appeared much the same but the incidence of sudden death and total mortality was significantly reduced in patients receiving alprenolol. These results have been questioned because of the use of a fixed dose regimen and the small sample size analyzed.

In the study by Ahlmark and co-workers a similar reduction in sudden death was seen in patients treated with alprenolol compared to matched controls. In contrast to the findings of Wilhelmsson and colleagues, these investigators also reported a reduction in the actual reinfarction rate in patients receiving alprenolol. This single blind randomized trial was carried out for two years in 162 patients who had sustained a myocardial infarction (Table 1). Patients received either 100 mg of alprenolol four times daily or no beta blocker. This study has been criticized on the grounds that the patients were randomized before their eligibility for the study was determined and because the study was open and the control group was not given placebo.

Alprenolol was well tolerated in the three trials as demonstrated by the low patient drop out rate because of drug intolerance. It was concluded that alprenolol could be safely admin-

istered to patients with acute myocardial infarction excluding those patients with conduction disease, active bronchospasm and congestive heart failure.

The largest trial of a beta adrenoceptor blocker to date in patients with myocardial infarction was a double blind randomized multicenter international study in over 3000 patients comparing practolol with placebo (Table 1). One to four weeks after an acute myocardial infarction fixed dose practolol (200 mg twice daily) or placebo was randomly assigned to patients. Unfortunately the trial was prematurely terminated after the reports of practolol toxicity emerged. However 330 actively treated patients and 336 treated with placebo were followed for over two years. A significant difference was found in the incidence of sudden death within two hours after the onset of symptoms—30 patients in the practolol group compared with 52 patients in the placebo group. There was also a significant difference in the total number of cardiac deaths. A non significant trend toward reduction in non fatal reinfarctions, 69 compared with 89, was also found. In this study the beneficial effects seem to be confined to patients with previous anterior wall myocardial infarcts and low diastolic blood pressures at entry. The study also showed a significant reduction in cardiac arrhythmias and in the incidence of angina pectoris with practolol.

The evidence in favor of a prophylactic or cardioprotective effect of beta adrenoceptor blocking drugs in the management of patients following myocardial infarction is persuasive. At least three possible mechanisms of action might be implicated. Chronic beta adrenoceptor block-

ade might prevent myocardial infarction by (1) reducing myocardial oxygen demands<sup>2</sup> and/or altering abnormal platelet aggregability,<sup>4</sup> (2) by preventing malignant arrhythmias during the initial phase of an infarction, and (3) by influencing the size of the ischemic area apart from the antiarrhythmic action of the beta blocker irrespective of whether infarction occurred.<sup>40</sup>

Would one beta adrenoceptor blocking agent provide a theoretical advantage over another in patients with acute myocardial infarction? With equal degrees of beta adrenoceptor blockade all the available agents are equally effective in the therapy of hypertension, arrhythmias and angina pectoris.<sup>1,2,41</sup> Alprenolol, a non cardioselective agent with membrane stabilizing activity and intrinsic agonist effects and practolol, an agent which has cardioselective and agonist activities without membrane depressant effects, both appear useful as cardioprotective agents. Therefore it would appear that if beta adrenoceptor blockade proved to be an effective treatment modality in patients with myocardial infarction all the beta blocking drugs could be interchanged with the exception of small differences in side effects.

The observations made with alprenolol and practolol need to be confirmed and extended to larger patient populations. There were major methodological problems with both the alprenolol and practolol trials. Currently the National Institute of Health is sponsoring a large multicenter trial (Beta Adrenoceptor Blocker Heart Attack Trial, BHAT) evaluating long term oral propranolol therapy in patients with myocardial infarction. This study was designed to eliminate some of the methodological problems of previous trials. Patients who meet entry criteria will be randomly assigned to receive placebo and propranolol treatment five days after infarction. Propranolol is titrated from 160 to 240 mg daily to achieve effective beta adrenoceptor blockade. Serum levels are being monitored and patients are observed for up to four years. A patient cohort of over 4000 is being evaluated. The data to be collected include the incidence of sudden death, non fatal reinfarction, fatal myocardial infarctions (not sudden death), non cardiovascular deaths, arrhythmias and angina pectoris. A similar multicenter trial comparing metoprolol (a cardio-selective agent) with placebo is now being planned.

These well-controlled studies will undoubtedly

yield conclusive results that will lay to rest the controversy. It is anticipated that adrenergic blockade will be proved to be safe and effective in the management of heart disease but also in the prevention of myocardial infarction.

## Conclusions

The results of experimental research suggest that beta adrenoceptor blockade may play an important role in the treatment of acute myocardial infarction. It decreases cardiac work and improves myocardial metabolism. The drugs are also effective antiarrhythmic agents.

Beta adrenoceptor blockers significantly reduce the symptoms of angina pectoris. It has not been shown to influence the prognosis in patients in primary prevention trials. In the treatment of acute myocardial infarction, however, some evidence suggests that chronic beta adrenoceptor blocker therapy can reduce the incidence of sudden death and reinfarction.

In the treatment of acute myocardial infarction, the effectiveness of beta adrenoceptor blockade depends upon the functional integrity of the heart. The more left ventricular function is maintained by the mechanical and contractile properties of ischemic areas, the more likely is beta adrenoceptor blockade to improve hemodynamic monitoring of patient response. The early use of beta adrenoceptor blockers to interrupt the stepwise development of myocardial necrosis may salvage myocardial tissue and improve immediate mortality rate and long-term ventricular function.

Future studies will determine whether adrenergic blocking drugs can enhance the quality of life as well as the quality of life of patients who have sustained a myocardial infarction.

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## Microscopy of urine—now you see it now you don't!

Nearly all presently performed routine microscopic examinations of the urine are practically useless and some results are dangerous.

The detection of abnormal numbers of casts, white or red blood cells in urine is probably the most sensitive index of the presence of urinary tract pathology, although for casts up to the present time this has not been studied in a thorough and systematic fashion with modern techniques. A simple calculation on the relation between the kidneys' tendency to hypertrophy after nephrectomy and presumably also after slowly progressive nephron destruction such as that due to glomerulonephritis, implies that even an accurately measured glomerular filtration rate will not show a change until about 40% of the nephron population has been destroyed. Therefore the earliest changes will only be detectable by histological examination of the kidneys or by accurate and careful examination of the urine.

However presently employed techniques of urinary microscopy by routine hospital and private pathological laboratories, whether by centrifugation of the urine and examination of the sediment on an ordinary microscope slide and reporting a per high power field (HPF) or by examination of an uncentrifuged specimen is in our experience useless and an enormous waste of public money. We have shown that with a semiquantitative technique employing centrifugation of the early morning specimen and examination of the sediment in a counting chamber good correlation can be obtained with renal functional abnormalities and abnormal numbers of casts, red cells and white cells in a single examination. When the same urine specimens were examined by the routine laboratory in a renally oriented hospital employing the HPF technique the correlation with renal functional abnormalities was much less. Particularly significant was the fact that in two out of four patients with histologically proven glomerulonephritis the HPF technique did not detect casts whereas the semiquantitative technique did so in all cases. Evaluation of the two techniques was retrospective and although not specifically blind the diagnoses were unknown at the time of renal functional testing and urine examination.

Increasingly frequent claims are being made of the presence of silent glomerulonephritis—i.e. histologically documented glomerulonephritis yet completely normal urine sediment. In our experience this is not so although a stressed before a systematic prospective study of this has not yet been performed. All previous studies have employed these unsatisfactory HPF methods. In this regard a recent report on severe Goodpasture's syndrome without significant renal pathology is of particular interest since the authors were unable to find abnormalities in the urinary sediment when examined by a technique similar to the ones proposed. Histology only showed mild linear immunofluorescent deposition but no light microscopic change. Whether the immunofluorescent deposition signified renal pathology of course is questionable.

A more recent practice is to examine an uncentrifuged specimen for white cells and red cells and express them as numbers per microliter of urine. Although this method has been shown to reflect reliably the number of cells per microliter particularly at high cell excretion rates it is entirely unsuitable for looking for casts—most physicians probably do not realize this and interpret a report showing no casts seen as reliably indicating no casts present in the urine. Although we have not quantitated our available data to compare the uncentrifuged data with our semiquantitative method as we did with the HPF method our impressions with another three hospital laboratories are that they are similarly unsatisfactory in detecting abnormal numbers of casts, white and red cells. This is of course not surprising. It is almost certain that presently employed routine techniques, unless performed by a nephrologist, are useless and lead to gross underestimation of renal pathology on the one hand and to a number of unnecessary renal biopsies on the other. Probably because it is believed that one can have a normal urine sediment with significant renal pathology. In our opinion these methods of examining the urine should be abandoned for it is far better not to have a result of a micro-urine examination than to have a false one. This is of particular importance when one considers the necessity to do renal biopsies. If urine microscopy when thoroughly examined shows no abnormalities no biopsy should be performed unless for academic reasons and with the full consent of the patient having had this situation explained to him. This is all the more important because of a recent prospective report that followed renal biopsies. Seventeen out of 90 had significant perirenal hematomas detected by CAT scanning.

Although for casts normal excretion rates are difficult to define because of the possibility of fragmentation of them in our experience the levels we have quoted of about 10 per mL seem a reasonable compromise. Normal values for white cell excretion rates are better defined and a level between 2000 and 3000 (2 to 3 per mL or 1 per HPF) per milliliter of white cells and 500 and 1000 (0.5 to 1 per mL, less than 1 per HPF) red cells per milliliter are acceptable normal limits. There may be some variation of urines during the day are examined rather than early morning specimens as the latter will of course be more concentrated.

These normal limits for this technique have now been defined in 120 volunteers without a history of renal disease (Personal communication Prof. D. Ferguson, School of Public Health Blood Pressure Study, Sydney, Australia). Preliminary analysis of these data showed that 95% had 3000 WBC/mL or less, 93% had 1000 RBC/mL or less and 99.6% had 10 casts/mL or less.

Addis was the first to introduce a scientific approach to quantify excretion rates of the formed elements of the urine. The upper limits of normal by this technique are however significantly lower at 8/mL for casts, 800/mL for WBC and

200 ml. for RBC presumably because of destruction of these elements when urine is collected and stored over 12 hour periods. The technique is cumbersome because of the necessity for a timed urine collection and the long time interval involved and it has been largely abandoned.

We would therefore urge that present methods of performing urinary microscopy with overuse and inaccurate results should be abandoned. The procedure should be performed by a nephrologist unless more stringent methodology is adopted by pathology laboratories. The excuse that these tests are being ordered too frequently is unsatisfactory; it is better not to do them than to give a wrong result.

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## Excess smoking in malignant hypertension\*

James VI of Scotland and I of England was the first to condemn smoking publicly when he stated that it was a "curious loathsome to the eye, hateful to the nose, harmful to the brain and dangerous to the lungs." Few of his successors to the throne took heed of his word and indeed we are told that the last four kings of Britain died of causes that may have been attributable to smoking. The list of such diseases is long and seem to be growing but until now hypertension has not been recognized. It has been shown that the act of smoking a cigarette causes a transient rise in blood pressure and that there is an increased mortality rate among smokers with hypertension but it has otherwise been demonstrated that smoking does not cause hypertension.

Two recent studies, however, one from Glasgow, Scotland and the other from Birmingham, England have shown that smoking is more common in a selected group of hypertensive subjects, namely those with malignant phase hypertension. By taking a diazole pressure greater than 120 mm Hg with bilateral retinal hemorrhages and exudates as the criteria for inclusion in their study the Glasgow workers identified 84 patients with malignant phase hypertension and found that 42 were smokers. By contrast only 4 of 107 of patients in three age-matched control groups smoked. These differences were significant for the sexes separately and together for cigarette smoking alone and for all forms of smoking combined.

As might be expected the malignant phase patient fared

worse than their non malignant controls in respect of failure and mortality. A more interesting observation was that smoking had a strong association with renal failure and mortality within the malignant phase group. The mean creatinine of the smokers ( $2.4 \mu\text{mol/L}$ ) was double that of non smokers ( $106 \mu\text{mol/L}$ ) of the 18 patients with creatinine greater than  $250 \mu\text{mol/L}$  1 were smokers and 17 an ex smoker. When deaths were considered, the overall mortality was confined to smokers. By contrast none of who had never smoked had died during follow up, a reached a mean of 3 years.

The Birmingham workers took as their criteria for malignant phase hypertension bilateral hemorrhages or exudates and studied 48 patients comprising whites, blacks, and Asians. They derived similar findings in that 60% were smokers in contrast to only 3% of controls who smoked. They reached significance for all groups with the exception of women alone. Both studies were performed retrospectively and in neither was it possible to say whether the cigarette smokers smoked was important.

These results suggest that smoking may precipitate malignant phase in a patient who is already hypertensive. This may explain at least in part the higher mortality from hypertension in smokers. Clearly smoking is not the cause of malignant hypertension as a cause of the patient never smoked. Most would agree that increased arterial pressure is the primary factor and it has been argued that increased arterial pressure promotes intra-arterial occlusion so leading to the main features of the disease. It could act as a trigger at this stage of the process by increasing platelet stickiness and viscosity of the blood.

\*This work was supported by the MRC Blood Pressure Unit, Western Infirmary, Glasgow, G6 7NT, Scotland. The authors thank requests for reprint should be addressed.

known to increase the likelihood of arterial thrombosis. The recently reported association of smoking with proliferative diabetic retinopathy may have a similar basis.

Whatever the mechanism, the message is clear. Smoking is commoner among patients with malignant phase hypertension. Patients with malignant phase hypertension who smoke are more likely to have renal failure and hence or otherwise are more likely to die. The case therefore for encouraging hypertensive patients already prone to cerebrovascular and ischemic heart disease to give up smoking becomes even stronger. James VI & I would certainly have agreed.

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## Drinking water and cardiovascular disease†

Nature has for centuries been conducting gigantic experiments as to the effect of climate, of type of work, of diet, and of local or world wide diseases on men, women, and children of different races that are spread out before our very eyes for us to record and to analyze, quite readily yielding information that might never be obtainable by our own experiments on man (quoted from P D White).

Man with his tremendous impact on nature has also produced uncountable experiments which are offered to the scientist as a precious material for investigation.

This annotation deals with a particular change in a natural situation due to human intervention which was brought to our attention in the course of the Seven Countries Study. This change gave us a unique opportunity to study the possible relationship between the quality of drinking water and cardiovascular disease.

This work was made possible by the consent of Dr A. Kessler, University of Minnesota, and the staff of the Seven Countries Study and by the grant from the WHO Grant No. C3/181/85.

†All statistical analyses were made at the Department of Chemistry, Memorial University of Newfoundland, St. John's, Canada.

In the frame of this study prevalence incidence and mortality rates for IHD and hypertension were studied from 1960 to 1975 in two population groups of men aged 40 to 59 years at entry living in two rural areas: Crevalcore and Montegiorgio respectively located in North and Central Italy. At the same time the characteristics of the drinking water of the two areas were also studied.

In Crevalcore the water was supplied since 1915 by an aqueduct in Montegiorgio construction started on an aqueduct able to reach all the peripheral areas of the community in 1960—the year of the beginning of our survey—and only during the next 5 to 10 years has this water supply gradually reached the most scattered farms and therefore the majority of the men belonging to the studied sample. This means that most people of Montegiorgio have employed for most of their life well and other spring waters and almost all until the age of 40 years or more.

The water of the wells in Montegiorgio was definitely a hard water (41.738 mg/L of CaCO<sub>3</sub>) and poor in zinc. The water of the aqueducts, both in Crevalcore and in Montegiorgio, was much harder (respectively 14.62 and 130.6 mg/L of CaCO<sub>3</sub>) and relatively richer in zinc. The change of water supply from



wells to aqueduct transformed Montegiorgio from 1960 to 1965 to "0—during the first 5 to 10 years of our survey—from an area supplied with a hard water poor in zinc to an area supplied with a relatively light water richer in zinc similar to the water supplied for a long time in Crevalcore.

Looking at the cardiovascular conditions of ischemic and hypertensive types in the two areas from 1960 to 1970 the impression does exist that higher prevalence of IHD and hypertension and the higher incidence and mortality rate for IHD existing at the beginning of the survey in Crevalcore are being rapidly followed by a catch up period in Montegiorgio whose IHD mortality rate during the last 5 years is definitely higher than in Crevalcore. The most impressive data concern cumulative IHD mortality rate which was 183, 222 and 443% per year in Crevalcore and 084, 111 and 417% in Montegiorgio at the three deadlines of 5, 10 and 15 years respectively. The increasing rates with time in both areas are due to the fact that they refer to a longitudinal study in other words to the aging effect.

A similar trend indicating the tendency of Montegiorgio to catch up to Crevalcore is shown also by the mean levels of blood pressure.

The information provided by these data is in agreement with the current hypothesis of the relationship between the

characteristics of drinking water and cardiovascular disease. As a matter of fact hardness, calcium and magnesium decreased and zinc is increased in Montegiorgio as compared to Crevalcore.

The available cases of morbidity and death are too few to provide statistical significance for IHD but only few suggestive conclusions. On the other hand the data on hypertension do reach statistical significance.

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## Of "now myocardial imaging"

The manufacturers of medical equipment too often dictate and even determine the nature of the practice of medicine and certainly the practice of cardiology. Manufacturers are responsible in large part for the extreme expense of the care of the sick. The use of the equipment and the cost to the patient are exponentially augmented by clinicians, laboratories, and hospitals. Some diagnostic procedures are not only unnecessary and costly but are even hazardous—the treadmill Holter monitoring though not hazardous is overused as well as the treadmill and now we can add to the already long list of procedures cardiac nuclear imaging the beginning of "Nuclear Cardiology." I have yet to see from personal experience

or from the literature where myocardial nuclear imaging has been shown to assist in any way in diagnosis and management of a cardiac patient. As a research procedure it may have application but as a procedure it has no real value at present and the patients should not be charged directly or indirectly myocardial imaging until its usefulness in service to patients is fully established.

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## Simplifying cardiopulmonary resuscitation rules

*to the Editor*  
Cardiopulmonary resuscitation (CPR) training is beamed at a wide range of people in all walks of life. Its rules therefore should be as simple as possible and they should be easily remembered. Most of the rules fit these mandates, yet some of them could be simplified.

The differences in rate of compression for one rescuer (40-60/minute) or a team of two (60 times/minute) add an avoidable complication. The rate for adults could as well be 60 compressions per minute, whether there is one rescuer or two. It is difficult during an emergency to exactly time the compressions. Another change to facilitate memorization refers to the ratio of compressions to required breaths (15:2 for one rescuer, 1:1 for two). This could be 10 to 2, whether there is one rescuer or a team.

Even the variations in the body sizes of victims, precision is meaningless and the figures provided for CPR are only approximations of what is optimal. It has been argued that a compression rate of 40 would be as effective as one of 60. The rules can be more complex for Emergency Medical Technicians (EMTs) but for those rarely called to do CPR, simplicity and ease of recall are more important considerations than small differences in rates.

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## Reducing complications with heparin therapy

*to the Editor*  
The authors of "Heparin therapy: A randomized prospective study" (AM HEART J 97:15, 1979) state that they found no incidence of bleeding complications to be the same in patients receiving intermittent as in those receiving continuous heparin therapy. Thus, the data regarding the relative frequency of bleeding complications with these two regimens continues to be debated. Some have concluded that there is a lower incidence of bleeding with intermittent therapy than with continuous administration, while others report no difference in bleeding complications between continuous and intermittent heparin therapy. One may assume after review that duration of therapy, age, sex, and trauma are probably more important determinants of hemorrhage during heparin therapy than method of administration. What then is one method of administration over another? Perhaps we should investigate the risk of thrombotic complications in relation to the method of heparin administration.

The pharmacokinetic studies of heparin report that the half-life of heparin in the usual clinical dose is approximately 2-3 hours. This would indicate that the administration of heparin at 4-hour intervals would result in the effective dose being equalled or exceeded for 1/2 of the 4 hours while for the other 1/2 hours the heparin level would be low. Therefore, heparin given by intermittent methods is subject to a course of

peaks and valleys indicating either excessive or under anticoagulation. This would imply that if one were to use the intermittent approach, the schedule of doses should be every 2 hours as opposed to the current trend of every 4 hours, but such a schedule is impractical. Also, the time of blood collection in relation to time of heparin administration for proper monitoring becomes very crucial when the degree of anticoagulation is rapidly changing in relation to heparin half-life.

Heparin pharmacokinetics illustrates a first-order function of the drug, which implies that the heparin clearance rate is independent of plasma concentrations or dose levels. But the disappearance of heparin is more complex because in normal subjects drug disappearance closely follows a zero-order function (the larger the dose of heparin, the longer the half-life, hence the lower the clearance). However, in the presence of thrombosis the clearance pattern changes, becoming closer to the first-order function. Moreover, in patients with pulmonary embolism there is a more rapid clearance of heparin and a shorter heparin half-life than with just venous thrombosis alone. Thus, heparin kinetics are altered in some way by the existence of thrombosis. The explanation appears to be unknown.

Therefore, one could conclude that heparin given by continuous infusion has advantages over the intermittent method. By using the continuous infusion method, the clinician is taking into account heparin's short half-life, its altered pharmacokinetics, and he is providing clinically useful antithrombotic plasma levels and avoiding long periods of either excessive or inadequate anticoagulation that may be encountered with the intermittent method, thus avoiding recurrent thrombotic episodes. This appears to be particularly important in patients with pulmonary embolism in that they exhibit increased heparin clearance. Also, the monitoring of anticoagulation dose may be drawn once a day instead of taking the APTT before each bolus dose of intermittent injection. In this way, the clinician is not subject to errors imposed by the APTT resulting from the peaks and valleys encountered with intermittent heparin administration.

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## HL A and hypertrophic cardiomyopathy

### To the Editor

We were interested in the findings of Matsumori and co workers of a lack of association of any histocompatibility antigen with hypertrophic cardiomyopathy in their study of 28 unrelated patients. This contrasts with the simultaneously published results of Darsee and co workers which show a marked association with HL A B12 in Caucasoids and with HL A B5 in negroes. It is notable that in the data of Matsumori and co workers both B12 and B5 were less common in the patients with hypertrophic cardiomyopathy than in the controls. Possibly the different findings in the two studies just reflect the different ethnic populations studied.

The finding of an association of hypertrophic cardiomyopathy with HL A A9 and HL A B7 within a family is of much lesser significance in terms of genetic linkage than would be a similar finding in unrelated subjects although the case is certainly strengthened by the finding in two separate families. The authors are rightly cautious in inferring that this association implicates an immune mechanism in the etiology of hypertrophic cardiomyopathy. However they cause considerable confusion when they quote two papers demonstrating that an autoimmune mechanism may be involved in the pathogenesis of some of the patients with cardiomyopathy. The evidence implicating autoimmune viral or other immunological mechanisms in the pathogenesis of hypertrophic cardiomyopathy is negligible. By contrast there is increasing evidence of viral and immunological mechanisms in the development of the quite distinct disease entity congestive cardiomyopathy. The term idiopathic cardiomyopathy should be avoided because of this confusion. It is essential to specify whether the cardiomyopathy is hypertrophic or congestive.

As a further minor point the continuity correction for the  $\chi^2$  test was first described by Yates not Yate. It is only usual to employ this correction in 2x2 tables which would not be applicable in the study of Matsumori and co workers.

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### Reply

#### To the Editor

We thank Drs MacArthur and McKenna for their comment on our work. HL A A9 and B7 are common in patients with hypertrophic cardiomyopathy. There was no significant difference between patients and controls. Darsee and co workers found significant association of HL A B5 in Negroes and HL A B12 in Caucasoids with hypertrophic cardiomyopathy. It is well known that the frequencies of HL A antigens vary greatly among different populations. It is conceivable that different susceptibility genes are in disequilibrium with different antigens. Although we found no significant association between HL A antigens and hypertrophic cardiomyopathy in the population study, the occurrence of hypertrophic cardiomyopathy was associated with a given HL A in first degree relatives of the affected family members.

Our observation suggests that a gene of the HL system was associated with hypertrophic cardiomyopathy in familial occurrence but the gene was not identical. It did not show a very high linkage disequilibrium with particular HL A antigens. Similar associations were found in the case of ragweed hay fever.

There is also the problem of disease heterogeneity. Hypertrophic cardiomyopathy may be a collection of different entities so any strong association between a susceptibility gene of the HL system and one entity would be obscured by the fact that a few entities included within the same category may not be associated with the same disease susceptibility gene.

Although further studies including studies of the DR loci are necessary to elucidate the role of the HL system in the pathogenesis of hypertrophic cardiomyopathy, HL A may be useful in the field of prognostic diagnosis of hypertrophic cardiomyopathy.

As Drs MacArthur and McKenna pointed out in our two previous papers, in which autoimmune disease was suggested in the pathogenesis of cardiomyopathy of the patients, it should be recalled that in the clinical cases reported in our paper of 1979.

ected classification or even definition of cardiomyopathy not established. This was before echocardiography was available. That is the reason why the term cardiomyopathy without mentioning the type classification hypertrophic or congestive was used in that paper. We of course agree with the opinion that the cardiomyopathy should be defined as either hypertrophic or congestive although it is sometimes difficult to do so even at present.

In our work statistical analysis was done by the chi square using a  $2 \times 2$  table, this is usually done in an investigation to evaluate whether there is a statistically significant difference between the frequencies of HLA antigens in patients and controls. Therefore Drs MacArthur and Kenna's last comment may not be pertinent. Lastly we thank them very much for correcting our spelling of Yates.

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**Circulation of the Blood** Edited by D Gerrant James Ballt  
more Maryland 1978 University Park Press 429 pages Price  
\$59 50

This book on the circulation of blood is appropriately published on the quadricentennial of the birth of William Harvey. The contributors are numerous each responsible for an aspect of the circulation. The subject is well reviewed including interesting things about William Harvey cerebral cardiac and pulmonary circulations circulation and disease of the aorta action of drugs lipoproteins cardiac surgery pathology of vessels and many other problems. The contributors are from all over the world mainly from England. This excellent book is certainly worth owning. It effectively reviews the biography of William Harvey and of the Harvey Society of New York but it also contains important papers on the circulation. The papers are well written and well chosen and the subject is certainly important. Surely the presentations are brief but they do reflect the opinions of the respective authors extremely well.

**Microcirculation Volume II** Edited by Gabor Kaley and Burton M Altura editor Baltimore Maryland 1978 University Park Press 26 pages Price \$52 50

This volume on microcirculation is excellent. Unfortunately a physician even those engaged in managing cardiovascular diseases do not understand or know the microcirculation. After all it is the small blood vessels that deliver the blood to living cells. This volume is divided into four main sections e.g. vascular smooth muscle regulation of the microcirculatory blood flow vascular responsiveness and comparative aspects of vertebrate microcirculation. The book consists of a number of papers concerned with the above subjects. This is a good review of selected aspects of the microcirculation. The book is highly recommended. Although complex in many parts the presentations are clear and concise.

**Exercise and the Heart** Edited by Nanette K Wenger MD  
Philadelphia L S F A Davis Company 246 pages

This is another timely issue of *Cardiovascular Clinics*. The recent interest in exercise in diagnosis and prevention and treatment of heart disease renders this book of general interest. The benefits of exercise in the prevention and management of heart disease are yet to be established and the value and need of its use in diagnosis remains controversial at least in the mind of many critical physicians. Physiologists and cardiologists however there are many who are fully convinced of its value in these phases of cardiology. This publication briefly summarizes very well the opinions and recommendations of the many who emphasize the value of exercise in the practice of cardiology. Therefore this book represents a good illustration of current views of the strong proponents of exercise in the primary and secondary prevention of cardiovascular disease as well as all the publications of *Cardiovascular Clinics* will be an excellent source of useful information in cardiology.

**Fibrinolysis** Edited by P J Gaffney and Ballt  
London 1978 Academic Press Inc London Ltd  
Price £ 9 50

This book contains papers presented at a symposium in Istanbul Turkey during September 1978. The papers discuss the kinetics of fibrinolytic agents as well as their pharmacological and therapeutic application. This is a very good book on the subject. Most of the contributors were from Europe. The practical clinical concept of the book should interest physicians in general as well as cardiovascular surgeons and other physicians. This is a good presentation on an important subject which reviews very busy clinicians in one volume the problem of fibrinolysis in therapy.

**Cardiovascular System Dynamics** Edited by Jan Buitendijk  
ham Noordergraaf and Jeff Paines Cambridge Mass  
The MIT Press 618 pages Price \$ 0 00

This book represents the symposium held at Hallam, Pennsylvania during April 1978. As with all symposiums the publication consists of a series of selected papers on the subject. The symposium was concerned with cardiac coronary circulation ventricular dynamics systemic arterial microcirculation systemic veins pulmonary vascular control mechanisms in specific vascular beds, cardiac system control, theoretical methods applied to the cardiovascular system, experimental methods applied to the cardiovascular system and cardiovascular instrumentation and computer simulation. The book consists of many papers presented by many contributors. Unfortunately, there were not a few papers with the reliability of the methods employed. Too frequently the data are accepted as sufficiently accurate to justify physiologic interpretations when this is not so. The questions and answers presentations are most interesting. The book summarizes very well the present concepts and practices in the study of cardiovascular dynamics and therefore it is of interest to those engaged in such investigations. Physicians and cardiologists should appreciate this book.

**The Essentials in Cardiac Pacing** An Illustrated Guide  
Guy Fontaine MD Yves Groggost MD Jean-Jacques Welts MD and Bernard Tardieu London and Paris  
Martinus Nijhoff Medical Division-The Hague 80 pages

This is a brief clearly written and illustrated discussion of the technique of cardiac pacing. The authors in a simple review extremely well the use of cardiac pacing. They cover the cellular electrophysiology anatomic and physiological disturbances responsible for the need of cardiac pacing. The equipment technique and indications are also discussed very well. This is a brief 80 page effective discussion of cardiac pacing.

**Medical Data Transmission by Public Telephone Systems**  
 Edited by Hans Jurgen V. Menden and Hanjorg Just  
 Baltimore 1978 Urban & Schwarzenberg 137 pages Price  
 \$100

**Cardiac Anesthesia** Edited by Joel A. Kaplan M.D., New  
 York 1978 Grune & Stratton Inc. 530 pages Price \$44.75

**Primary Care Judgments of Nurses and Physicians** Volumes  
 II and III By Frank M. McLaughlin Harold G. Johnson  
 Thomas A. Cesa Mary M. Lemons Sara J. Anderson Patricia  
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**Embryology and Teratology of the Heart and Great Vessels**  
 By C. H. S. van Mierop A. Oppenheimer Dekkers, and C. L.  
 D. C. Bruuns, The Hague The Netherlands 1978 Martinus  
 Nijhoff Publisher 224 pages

**Cardiovascular Effects of Mood Altering Drugs** By Barry  
 Stimmel, M.D. New York 1979 Raven Press 290 pages

**Cardio-Vasculaires** By R. Froment P. David J. P. Delahaye  
 J. Descotes A. Gouin P. Michaud and J. Normand Paris  
 New York Barcelona and Milan 1979 Masson & Cie 330  
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## Symposium on Dynamic Radionuclide Cardiac Studies

A symposium entitled "Noninvasive regional wall motion evaluation using dynamic radionuclide cardiac studies" from underlying principles to practical applications will be presented in Chicago, Ill. on April 18 and 19, 1990. Sponsored by the University of Illinois College of Medicine, Abraham Lincoln School of Medicine, Department of Radiology, Section of Nuclear Medicine, the symposium is designed for nuclear medicine physicians, cardiologists, and others who desire to improve their knowledge of the latest techniques involved in these radionuclide studies. The guest faculty will include speakers of national and international renown. Formal lecture presentations, case presentations, round table discussions, and workshops are featured on the agenda. Registration fee for the symposium will be \$100 for physicians and \$50 for residents and fellows. The symposium is approved for 12 hours of AMA Category 1 credit toward the Physicians Recognition Award of the AMA. For further information, contact: University of Illinois at the Medical Center, Office of Continuing Education Services, 1853 W. Polk St., Room 144, Chicago, Ill. 60612. Telephone: (312) 599-8072.

## Symposium on Clinical Trials

The First Annual Scientific Session, Society for Clinical Trials, and the Seventh Annual Symposium for Coordinating Clinical Trials will have a combined meeting on May 6 through 8, 1990, in Philadelphia, Pennsylvania. The sessions will focus on the design, organization, management, and analyses of clinical trials. For further information, write: Christine R. Klumt, M.D., Secretary, Society for Clinical Trials, Inc., 600 Wyndhurst Ave., Baltimore, Md. 21210.

## Symposium on Radiology

A symposium entitled "Radiology Today—A Multinational Symposium" will be held on June 12 through 15, 1990, in Salzburg, Austria. This symposium, conducted in English, is bringing together consultants and radiologists from Europe and the United States for a review of the most recent advances in diagnostic radiology, nuclear medicine, and ultra-sound. A concise review of each specialty area of diagnostic radiology spanning the last two years will be presented. It will include panel discussions and informal workshops focusing on the integration of these recent advances into the patient's care. For further information, contact: Dr. Martin W. Dorer, Johns Hopkins Hospital, Baltimore, Md. 21205.

## Asian Pacific Symposium on Cardiac Pacing

The First Asian Pacific Symposium on Cardiac Pacing will be held in Jerusalem, Israel, from June 16 through 19, 1990. The symposium will deal with recent advances in the field of Cardiac Pacing (technology, follow-up, rare indications, functions, medico-legal aspects, and others). There will be commercial exhibits and a special program for acceptor persons. For further details, write: The Secretariat for Asian Pacific Symposium on Cardiac Pacing, P.O. Box 10, Tel Aviv, Israel.

## Editorial

### Necrotizing vasculitis: coronary anginitis and the cardiologist

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Many diseases in medicine produce as much diagnostic and therapeutic consternation as the problem of vasculitis. Because of its varied modes of presentation it is considered in the differential diagnosis of many perplexing multisystem diseases. However, because few clinical tests apart from biopsies are absolutely characteristic, vasculitis is a difficult diagnosis to establish and in some cases is made only at autopsy. The cardiologist may be confronted with the difficult task of differentiating the vascular stenosis of atherosclerosis from that of inflammatory vasculitis. Recent developments have made this differentiation critical since a number of vasculitic syndromes are now responsive to a variety of therapies. The present article will briefly review recent advances that have occurred in the classification, pathogenesis and treatment of necrotizing vasculitis with special emphasis on coronary arteritis.

The classification of the different vasculitic syndromes has been one of the most confusing in medicine. This has been partially true because the categorization has been done on the basis of pathologic studies which commonly bear little

relevance to the clinical presentation and partially because there is much overlap among the various vasculitic syndromes and many patients cannot be easily placed into one category.<sup>1,2</sup> Thus many authors have written about the spectrum of vasculitis<sup>3</sup> and some have argued that all vasculitis should be termed necrotizing vasculitis and classification should only be used for historical interest. However, despite the unquestionable overlap among the vasculitides there are some well described syndromes with clear cut natural histories and responsiveness to different therapies and therefore it is our opinion that appropriate classification is worthwhile to the clinician.

Table I lists the various vasculitic syndromes, some of which are well defined and others of which have considerable overlap with one another (see below). A recent review has delineated the clinical and pathologic presentations of the different types of vasculitis.

The vasculitic syndromes of most importance to the cardiologist are those that primarily involve the coronary arteries and/or the aorta. Thus Takayasu's arteritis, the mucocutaneous lymph node syndrome (MLNS), polyarteritis nodosa (PAN) and vasculitis associated with certain collagen vascular diseases are the vasculitic syndromes that should be very familiar to cardiologists. Although aorta and/or coronary arteries have been reported to be involved in temporal arteritis or Wegener's granulomatosis,<sup>4</sup> these are rare occurrences.

Takayasu's arteritis or pulseless disease

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Received for publication on April 30, 1979.

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Table 1 Classification of vasculitis

	Clinical presentation	Pathology	Diagnostic workup	Treatment
Polyarteritis nodosa (PAN)	Multorgan dysfunction especially of kidney gastrointestinal tract heart and peripheral nervous system Commonly accompanied by generalized systemic complaints—fever weight loss, arthralgias/myalgias. In fulminant form may overlap with MCLS	Necrotizing vasculitis with fibrinoid necrosis of small and medium sized muscular arteries Lung and spleen characteristically spared Microaneurysms characteristic	Arteriography Or organ biopsy Linked in significant number of cases (~30%) to hepatitis-B infection	Corticosteroids Cytotoxic therapy
Allergic granulomatosis (Churg and Strauss)	Previous allergic history usually asthma eosinophils pulmonary infiltrates also involves heart kidney GI tract and peripheral nerves	Necrotizing vasculitis with eosinophils and granuloma formation of small and medium-sized muscular arteries as well as capillaries and venules	Arteriography Biopsy (especially of lung)	Corticosteroids Cytotoxic agents
Hypersensitivity vasculitis primary or secondary	Most confusing and heterogeneous category of vasculitis Most commonly involved organ is skin with palpable purpura, urticaria or wide variety of skin lesions. May involve only skin or may involve many organs to variable degree—kidney heart GI tract Has been linked to drug ingestion, certain bacterial infections ( <i>Streptococcus</i> ) or may occur with out precipitating cause	Necrotizing vasculitis of small vessels especially postcapillary venules with neutrophil infiltration nuclear debris (leukocytoclastic vasculitis) fibrinoid necrosis and erythrocyte extravasation	Biopsy	Withhold all drugs (except aspirin)
Wegener's granulomatosis	Sinusitis, pulmonary nodules and glomerulonephritis	Necrotizing granulomatous vasculitis of medium and small vessels of upper and lower respiratory tract necrotizing glomerulonephritis	Biopsy of involved organs	Cytotoxic therapy
Temporal arteritis	Disease of elderly Fever poly myalgia rheumatism headache visual difficulty	Giant cell panarteritis of arteries of carotid system (especially temporal artery)	Temporal artery biopsy	Corticosteroids (daily) to effect
Takayasu's arteritis	Young women most commonly affected Early disease produces generalized systemic symptoms. Late disease symptoms related to large vessel (subclavian carotid) occlusion	Granulomatous panarteritis particularly of aortic arch and large branches also may affect pulmonary artery Occasional giant cells	Aortography Biopsy difficult because involved vessels inaccessible	Corticosteroids prophylactic therapy immunosuppression
Mucocutaneous lymph node syndrome (MCLS)	Infants and young children Fever cervical adenitis conjunctivitis erythematous-desquamating rash of skin and mucous membranes. 1-2% die due to coronary arteritis	Coronary arteritis most common with aneurysm formation and myocardial infarction due to coronary occlusion	Coronary angiography	Prophylactic corticosteroids (daily) to prevent aneurysm formation
Buerger's disease	Seen largely in young adult males Peripheral arterial insufficiency in cigarette smokers	Intermediate and small arteries of upper and lower extremities. Thrombus formation with polymorphonuclear infiltration	Arteriography	Abstinence from cigarette smoking
Arteritis of rheumatic fever	Fulminant acute rheumatic fever	Associated with Aschoff bodies Small arteries of heart and lung most involved	Workup for acute rheumatic fever	Subcutaneous corticosteroids

argely a disease of young women with predilection for the aortic arch and its major branches as well as relatively frequent (up to 50 per cent in series) involvement of the pulmonary arteries.<sup>13</sup> This vasculitis appears to have two broad clinical presentations—one characterized by generalized malaise headache paresthesias and generalized signs of active inflammation. The second presentation is due to locally occluded vessels and subsequent ischemia of arms legs or brain.<sup>10, 11</sup> A recent report has related four complications of the disease—retinopathy, secondary hypertension, aortic regurgitation or aneurysm formation—to ultimate prognosis. All of the patients who died of Takayasu's arteritis had at least one and usually two or more of these complications. Establishing a diagnosis can often be difficult since the involved vessels are often large and relatively inaccessible to biopsy. Diagnosis usually depends upon arteriographic demonstration of tubular vessel narrowing in a clinical setting where atherosclerosis is unlikely. Corticosteroids are efficacious in ameliorating the general systemic symptoms and signs of the disease,<sup>1</sup> and some authors have reported return of flow to previously pulseless extremities,<sup>11</sup> however results of corticosteroid trials have been variable especially when extremity or organ ischemia has been the major disease manifestation. Careful clinical therapeutic trials will be needed to determine whether corticosteroids (or cytotoxic agents) will be capable of preventing the complications of the disease which have been related to a poor prognosis. Surgical vascular reconstruction,<sup>12</sup> and aortic valve replacement for aortic regurgitation have been successfully employed in a small number of cases.

The MLNS or Kawasaki's disease is an extraordinarily interesting form of vasculitis originally recognized in Japan only 10 years ago. MLNS has considerable import to cardiologists because of its peculiar predilection for coronary vessels. Largely a disease of infants and young children the syndrome manifests itself as fever, bilateral conjunctival infection, erythematous scaling rash of the skin of the extremities, involvement of the oral mucous membranes and non-suppurative swelling of the cervical lymph nodes.<sup>1, 14</sup> Other less characteristic associated acute symptoms and signs have been myocarditis or pericarditis, diarrhea, arthritis, proteinuria and signs of inflam-

mation (increased sedimentation rate, C reactive protein but negative anti streptolysin O). The prognosis of this acute syndrome is usually good. However, 1 per cent to 2 per cent of patients will die suddenly, commonly in the recovery phase of the acute illness. At autopsy the cause of death is coronary arteritis commonly with aneurysm formation and coronary thrombosis with extensive myocardial infarction.<sup>16</sup>

A recent study has ominously reported abnormalities of angiographically determined coronary artery anatomy in 12 of 20 patients during and up to 4 years after acute MLNS.<sup>15</sup> Seven of the 20 had coronary artery aneurysms. Two patients showed regression of the coronary aneurysms at subsequent angiography and one patient developed mitral regurgitation as a result of papillary muscle dysfunction. Another report<sup>17</sup> found electrocardiographic abnormalities in 40 to 54 cases (74 per cent) with MLNS and angiography showed abnormalities in 14 of 17 (82 per cent) patients studied. Of the total of 72 patients in this report, eight developed mitral regurgitation and/or progressive congestive heart failure (CHF). Three patients died with progressive CHF and a fourth patient died suddenly. These studies suggest that involvement of the coronary arteries may be much more frequent than the original autopsy studies suggested. Apparently in some patients the coronary arteritis can spontaneously remit; in other patients the arteritis causes aneurysm formation and/or thrombosis. The natural history of asymptomatic coronary artery involvement remains unclear at present and will require careful follow up of these patients.<sup>18</sup>

Ventricular function in MLNS patients with coronary involvement can show segmental contraction abnormalities secondary to myocardial infarction or generalized hypokinesia presumably secondary to myocarditis.<sup>19</sup> Two dimensional echocardiography has been recently employed to non-invasively visualize coronary aneurysms in patients with MLNS.

Pathologically essentially all patients dying of MLNS showed active and healing coronary arteritis with intimal proliferation, fibroid necrosis and multiple aneurysms. Although arteritis of other vessels can be seen the coronaries are by far the most frequently involved. In addition the hearts commonly demonstrated myocarditis and pericarditis that could not be ascribed to ische-

mia. Because of the histopathologic similarity of this MLNS coronary arteritis to that of infantile PAN, some authors have concluded that they are the same disease.<sup>22</sup>

A clinical approach to the management and therapy of this disease is very difficult because only a small percentage of those stricken with the acute syndrome will develop clinical heart disease and an even smaller percentage will die from the disease. The recent report of coronary aneurysm visualization of noninvasive cross sectional echocardiography<sup>23</sup> provides a method of evaluating every patient with MLNS to assess the possibility of coronary involvement. However, the sensitivity of this procedure still needs to be determined. Furthermore, the prognostic significance of asymptomatic aneurysms is unknown and an effective mode of treatment is also not proven. Although corticosteroids may be helpful in symptomatically improving the acute syndrome, their effect on the coronary arteritis is unknown. Cytotoxic agents are untried and are difficult to employ in infants and young children.<sup>24</sup> A number of successful coronary artery bypass operations have been reported in patients with coronary aneurysms,<sup>25-27</sup> but the proper indications for this operation in MLNS and the long term effects are presently unknown.

Classic PAN is a systemic necrotizing vasculitis of small and medium sized muscular arteries of many organs but most commonly involving arteries in the kidney, gastrointestinal tract, heart and peripheral nervous system. Histopathologically, muscular arteries are involved by a panarteritis with neutrophil (later mononuclear) infiltration, fibrinoid necrosis and characteristic aneurysm formation. As originally described and classified, PAN did not involve pulmonary vasculature and eosinophilia and an allergic history were uncommon. In contradistinction, classic allergic granulomatosis reported by Churg and Strauss is a vasculitis of muscular arteries as well as small arterioles, capillaries and venules. Lung involvement is the rule rather than the exception. Most patients have a preceding history of asthma and eosinophilia and granulomatous reactivity is common. Many patients with systemic necrotizing vasculitis do not classify into either of these disorders and are considered to have an "overlap" syndrome—commonly with some features of hypersensitivity vasculitis (see Table I) as well. Because many patients (in some

series the majority) fall into this overlap syndrome, attempts at strict classification of these types of vasculitis are often not possible. This entire group would best be considered in the broad category of severe systemic necrotizing vasculitis.

Coronary arteritis is a frequent finding in patients with classic PAN, allergic granulomatosis, or the overlap syndrome. In a review<sup>28</sup> of 67 cases of polyarteritis nodosa (defined as a severe generalized necrotizing angitis) autopsy over a 32 year period, coronary arteritis was found in 62 per cent and usually involved both large muscular arteries and smaller vessels. Myocardial infarction was found also in 62 per cent of these patients and was acute in 50 per cent of those with infarcts. CHF was a common problem in these patients, probably secondary to myocardial infarction and hypertensive heart disease. CHF was felt to be the cause of death in 44 per cent of the 66 patients demonstrating cardiac involvement in systemic vasculitis. It is frequent (in this series the most frequent) cause of death.

Interestingly, myocardial infarction was diagnosed clinically in only three patients, although it was found at autopsy in some 41 patients. CHF was the most common clinical presentation of myocardial infarction. Thus, heart failure in the setting of generalized vasculitis should make one suspect that coronary arteritis may be producing a silent myocardial infarction. In this series, myocarditis was found in only 3 per cent of cases and was considered to be clinically insignificant.

The natural history of necrotizing vasculitis of the polyarteritis type was that of progressive multisystem organ dysfunction usually leading to death.<sup>29</sup> In retrospective studies, corticosteroid therapy has been associated with an improved 5-year survival from 13 per cent in untreated patients to 48 per cent in those treated with corticosteroids.<sup>30</sup> Because of our success at treating patients with Wegener's granulomatosis with the cytotoxic agent cyclophosphamide<sup>31</sup> and because of data suggesting that corticosteroids alone are ineffective in over half of patients with PAN, patients with necrotizing vasculitis of PAN type at NIH have been treated with cyclophosphamide usually together with corticosteroids immediately upon diagnosis. Seven of 11 patients have achieved long-term remissions and most of the failures were

patients whose disease was far advanced with considerable end organ damage. Thus it seems that cytotoxic agents with or without corticosteroids are more efficacious than corticosteroids alone in treating severe necrotizing vasculitis of the PAN group.

Although almost all of the collagen vascular diseases have been associated with some form of vasculitis the three collagen diseases most commonly complicated by systemic vasculitis are acute rheumatic fever, rheumatoid arthritis and systemic lupus erythematosus. The coronary arteritis of acute rheumatic fever is usually seen in severe episodes of this disease where diagnosis by Jones criteria is relatively obvious.<sup>3</sup> However the coronary arteritis of rheumatoid arthritis may be very difficult to diagnose. A number of series have shown that coronary arteritis may be seen in as many as one fifth of patients autopsied with rheumatoid arthritis, usually as part of a widespread diffuse vasculitis of many organs.<sup>2,3</sup> In rheumatoid arthritis a small vessel hypersensitivity vasculitis is more commonly seen than a large vessel PAN like vasculitis; the latter occurring predominantly in patients with seropositive erosive arthritis, subcutaneous nodules, and episcleritis. Although some original reports<sup>2,3</sup> suggested that corticosteroid therapy precipitated or worsened the arteritis of rheumatoid arthritis, more recent studies have shown that this is probably not correct. Rather vasculitis is a manifestation of severe rheumatoid arthritis which is more likely to be treated with corticosteroids. In most instances the coronary arteritis of rheumatoid arthritis does not produce clinical cardiac dysfunction. However CHF, myocardial infarction and sudden death have been reported.<sup>4,5</sup> Treatment of the vasculitis of rheumatoid arthritis has been generally directed at the underlying disease usually with corticosteroids and/or cytotoxic agents.<sup>1</sup>

Systemic lupus erythematosus can affect the heart in a number of ways—myocarditis, endocarditis, pericarditis, aortic insufficiency, hypertensive heart disease (frequently due to renal insufficiency) and coronary arteritis.<sup>6</sup> Coronary arteritis induced myocardial infarction has been reported but is considered to be rare.<sup>7,8</sup>

A very intriguing and important finding is markedly accelerated atherosclerotic coronary artery disease (as well as other vessels) in patients with systemic lupus erythematosus.<sup>9,10</sup> Buckley

and Roberts<sup>11</sup> argue that this premature atherosclerosis was secondary to the corticosteroid therapy. However their data are also just as consistent with the possibility that corticosteroids suppressed the extracardiac manifestations of systemic lupus erythematosus and allowed their patients to live long enough to develop diffuse atherosclerosis associated with factors directly or indirectly related to the underlying disease.<sup>9,12</sup>

Viral induced vascular injury either directly or through the immune response has also been postulated to predispose one to accelerated atherogenesis.<sup>13</sup> A recently developed animal model has demonstrated that viral infection can predispose certain animals to develop premature atherosclerosis.<sup>14</sup> Thus the vasculitis of systemic lupus erythematosus as well as any generalized vasculitis represents a double threat: first the acute vasculitis may produce enough vessel injury to cause acute inflammatory narrowing and tissue ischemia; second the arterial injury serves as a nidus for accelerated atherosclerosis which further narrows vessels resulting in premature arteriosclerotic occlusions. Some authors have suggested that inflammatory vascular changes may underlie much of the premature atherosclerosis seen in young patients.

#### Pathogenesis and etiology of vasculitis

The pathogenesis and etiology of most human vasculitis is not completely understood. However experimental animal models of immune complex vasculitis and chronic viral infection combined with recent demonstrations of viral infections associated with human vasculitis have provided strong evidence for the importance of immune mechanisms and viral infection in human arteritis. Most of human vasculitis is probably mediated via intravascular immune complex formation in antigen excess and entrapment of these complexes along the basement membrane of vessel walls with activation of complement components. Defective reticuloendothelial clearance of complexes may be important in pathogenesis. Complement derived chemotactic factors promote accumulation of polymorphonuclear leukocytes which release lysosomal enzymes and damage vessel walls. From experimental models it would appear that certain animals (perhaps humans) are genetically predisposed to produce the type of immune response that will culminate in inflammatory vascular damage.<sup>15</sup> Other mech-

anisms of immune damage (e.g. cellular or IgE mediated) have been postulated to produce vasculitis but the evidence is inconclusive.

The source of antigenic stimulation in human vasculitis is quite variable. In some cases exposure to a drug or a microbial infection appears to clearly precipitate a bout of vasculitis. Thus sulfonamide ingestion and streptococcal infections<sup>1,2</sup> have been associated with hypersensitivity type vasculitis. The association of amphetamine abuse with systemic vasculitis<sup>3</sup> may be another example of drug induced immune complex vasculitis in humans.

Chronic viral infection has been shown to produce immune complex mediated vasculitis in a number of animal models. In humans hepatitis B infection has been reported in up to 40 per cent of cases of necrotizing vasculitis. Circulating immune complexes and vessel wall deposition of hepatitis B antigen immunoglobulins and complement have been demonstrated in a number of these patients. The recent report of serous otitis media associated with systemic necrotizing vasculitis raises the possibility that an as yet unidentified microorganism probably viral causes serous otitis media and precipitates vasculitis.

The MLNS has many features of a serum sickness like immune complex reaction (rash, fever, arthralgias, lymphadenopathy) and a subset of patients (as in experimental models of immune complex disease) appear to develop the serious complication of arteritis usually of the coronary vessels. The fact that coronary arteritis is commonly found in the recovery phase of the acute syndrome suggests that the immune response rather than the actual infection may be responsible for the arteritis. Although rickettsia like organisms have been reported to be demonstrable in certain tissues in this disease, these reports have not yet been confirmed. The recent report of elevated IgE levels in MLNS is of particular interest. One could speculate that a rickettsial (or viral infection) is responsible for the acute syndrome of rash, fever etc. of MLNS. Some patients might have a genetic predisposition to produce an immune response that results in large amounts of circulating immune complexes in large amounts of circulating immune complexes in large amounts of circulating immune complexes could deposit in coronary vessel perhaps facilitated by IgE mediated reactions causing increased vessel permeability. These immune complexes

might then produce an inflammatory response, vessel damage, aneurysm formation and subsequent coronary occlusion.

In systemic lupus erythematosus, rheumatoid arthritis and essential mixed cryoglobulinemia immune complexes have been shown to mediate many of the disease manifestations. The fact that signs of active disease (circulating immune complexes, low serum complement levels, cryoglobulinemia or high titers of rheumatoid factor) are commonly associated with vasculitis lends further support to the concept that immune processes mediate vessel damage in many human vasculitides.

## Conclusion

In conclusion it is important for the cardiologist to be familiar with the clinical syndromes of vasculitis so that the appropriate diagnostic tests are performed. Vessel inflammation can be mimicked by atherosclerotic occlusive disease and predispose to premature atherosclerosis. Previous advances in understanding certain of the pathophysiologic mechanisms of some of the acute necrotizing vasculitides suggest that most forms of vasculitis are probably capable of being suppressed by an appropriate immunosuppressive therapeutic regimen. Therapy is most effective against active progressive early vasculitis. Once end organ damage has occurred reversibility of suppression with corticosteroids and/or cytotoxic agents is less effective. Thus early diagnosis of paramount importance to the control of these diseases. Tissue biopsy and/or angiography should be performed early to establish a diagnosis so that appropriate therapy can be instituted before severe end organ damage has ensued.

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### Correlation of the location of coronary arterial spasm with the lead distribution of ST segment elevation during variant angina

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Angina pectoris associated with transient ST segment elevation (variant angina) is usually due to localized transmural myocardial ischemia resulting from temporary severe obstruction or occlusion of a major coronary artery due to vasoconstriction or spasm of an epicardial portion of that vessel. Localization of the involved coronary artery helps to clarify the pathophysiology of a patient's attacks and to plan appropriate therapy. Coronary arteriography during a spontaneous or provoked attack of angina is the most reliable way to accomplish this but is not feasible in every case. A multilead electrocardiogram (ECG) made during an attack although not always easy to obtain exposes the patient to less expense risk and discomfort than does coronary arteriography and is frequently available before the latter procedure is undertaken. Although it seems likely that a multilead ECG made during an attack would be very helpful in localizing the involved coronary artery or arteries this supposition has never been critically examined.

#### Materials and methods

No one investigative group of physicians by itself has enough complete observations on variant angina patients in order to address this

problem. In my own observations of 62 variant angina patients there were only eight patients for whom all of the following data were available: (1) a multilead ECG recorded during the course of an attack of variant angina; a full 12 lead ECG was not required providing that sufficient leads were present to generally localize the ST elevation to the inferior anterior or lateral distributions; (2) a multilead ECG in the absence of angina recorded before or after the anginal attack for comparison; (3) coronary arteriography during an attack of myocardial ischemia produced by documented acute coronary artery obstruction or occlusion resulting from severe coronary artery vasoconstriction or spasm involving only one major coronary artery. The multilead ECG need not have been recorded at the same time as the arteriogram providing that there was some evidence that myocardial ischemia was present during the episode of coronary vasoconstriction (angina or ECG changes). This episode of myocardial ischemia could be spontaneous or iatrogenically provoked (e.g., by ergonovine maleate, methacholine or exercise).

From a review of over 1700 cases of variant angina published in the literature an additional 102 patients were selected for whom the above data were available.<sup>1-44</sup>

Data from this combined group of 110 patients (group A) was used to study the correlation between the location of the coronary arterial constriction or spasm during myocardial ischemia and the distribution of acute ST segment elevation on the ECG.

Another group of 20 cases from my own patients and 94 others from the published literature was selected to form a group of 114 patients

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Table 1 Lead distribution of ST segment changes observed during variant angina related to coronary arterial spasm

ECG lead	Right CA spasm (n = 57)			Anterior descending CA spasm (n = 39)			Circumflex spasm (n = 11)	
	No of cases showing			No of cases showing			No of cases showing	
	ST elevation	ST depression	No ST change	ST elevation	ST depression	No ST change	ST elevation	ST depression
I	0	12	43	9	0	4	0	2
II	55	0	1	1	0	5	13	1
III	55	0	1	0	5	6	17	0
aV <sub>L</sub>	0	2	53	0	0	10	0	3
aV <sub>R</sub>	0	16	39	11	0	2	0	5
aV <sub>F</sub>	56	0	1	0	6	5	12	0
V <sub>1</sub>	2	11	6	21	0	13	0	4
V <sub>2</sub>	0	10	7	35	0	1	0	3
V <sub>3</sub>	0	11	8	36	0	1	0	2
V <sub>4</sub>	0	11	8	32	0	5	0	1
V <sub>5</sub>	3	8	9	17	2	15	5	1
V <sub>6</sub>	5	5	9	9	2	22	4	0

\*The number of total cases showing either ST elevation, depression or no change in any lead is less than the total number of patient findings in that lead.

†Findings in a case of CA spasm limited to a marginal branch of the circumflex CA. ST elevation was limited to Leads V<sub>1</sub> and V<sub>2</sub>.

Abbreviation: CA = coronary artery

(group B) in whom relatively more complete ECG data were available before and during attacks of variant angina in order to establish in what leads the greatest degree of ST segment elevation was observed. All of these patients had had coronary arteriography but demonstration of artery spasm was not required.

I shall use the term coronary arterial spasm in this article to refer to the production of acute transient obstruction (or worsening of a pre-existing organic obstruction) in an epicardial coronary artery as the result of contraction of the vascular smooth muscle in its wall. The reader should be advised that this is a convenience and not be misled into thinking that all coronary arterial spasm implies hyperreactivity of the vascular smooth muscle. In the presence of important thickening of the vascular wall or of pleasurable organic stenosis normal amounts of smooth muscle contraction can produce severe obstruction or complete occlusion.

## Results

Location of ST segment shift in relation to coronary spasm. Coronary arterial spasm causing either ischemic ST segment shift or angina or both produced complete occlusion of the vessel in

54 cases produced 90% to 99% diameter in 36 cases produced 80% to 89% stenosis cases and resulted in 70% to 79% stenosis cases (severity of spasm caused stenosis specified in 10 cases).

In Table I are shown the data relating distribution of ST segment changes during variant angina to the observed site of coronary arterial spasm in the 110 patients in whom was actually observed in only one vessel. A) Transient ST segment elevation in Lead I and aV<sub>L</sub> was almost always present attacks in patients demonstrated to have spastic obstruction of the right coronary. One patient of mine had complete spastic obstruction of the proximal part of a dominant coronary artery (Fig 1) at which time he showed only upright peaking of a pre-inverted T wave in Lead aV<sub>R</sub> and ST segment depression in Lead V<sub>1</sub> (Fig. 2) there was significant ST segment elevation despite absence of visible collateral circulation on subsequent left coronary visualization after subsiding of the attack. This patient was never seen manifest significant ST segment elevation in 12 lead ECG during spontaneous anginal attacks.

On the other hand ST segment elevation

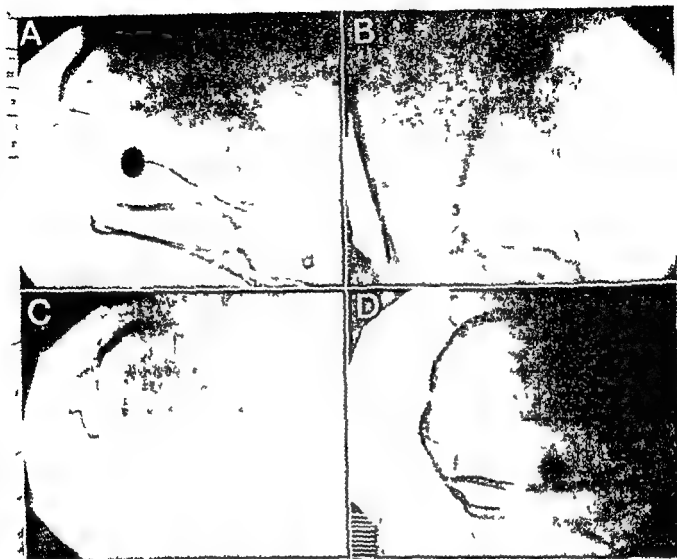


Fig 1 Selective arteriograms of the right coronary artery in a 51 year-old woman with clinical symptoms of variant angina. A Left anterior oblique (LAO) projection prior to onset of symptoms demonstrates an 80% stenosis (arrow) in the anterior portion of the vessel with rapid and complete opacification of the distal vessel. B Right anterior oblique view in the absence of symptoms shows the same stenosis, which here appears only 60%. C LAO view during the height of a spontaneous anginal attack shows complete occlusion of the vessel at the site of previous stenosis. The distal vessel is not visualized. PEG at this time did not show ST segment elevation (See fig 2). D LAO projection 3 minutes after relief of angina by sublingual nitroglycerin. The vessel is again patent but the organic stenosis persists.

Leads 2, 3 and  $aV_r$  was not specific for acute right coronary artery obstruction since it also occurred in almost all cases of severe circumflex coronary artery spasm as well. Whereas a dominant left coronary artery circulation was present in most of these cases, it was not a necessity in order for circumflex spasm to produce ST elevation in inferior leads. When ST segment elevation was present in inferior leads as the result of right or circumflex coronary artery spasm, it was

almost always present simultaneously in Leads 2, 3 and  $aV_r$ .

ST segment elevation in lateral precordial leads ( $V_4$  and  $V_5$ ) concomitant with inferior ST segment elevation (2, 3 and  $aV_r$ ) was present in a few cases of right coronary artery spasm but was relatively more common with circumflex coronary artery spasm. This finding did not really help to differentiate between the two vessels.

ST segment elevation in Lead  $V_1$  along with

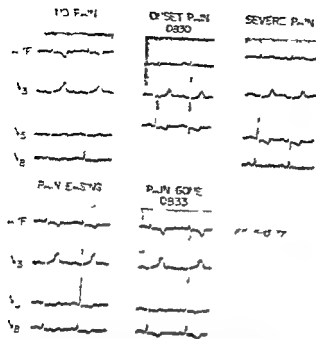


Fig. 2 Selected ECG leads recorded during coronary arteriography of the same patient whose angiograms are shown in Fig. 1. During the height of her anginal attack, immediately prior to the arteriogram shown in Fig. 1C the following changes were noted: previously depressed ST has become isoelectric and previously inverted T has become upright in Lead aV<sub>L</sub>; previously elevated ST in Lead I has become slightly depressed; previously isoelectric ST has become depressed with new T inversion in Lead I. T-U fusion is present in Lead I. These are the maximum ST and T wave changes seen during any of her anginal attacks. After subsidence of the attack, the ECG reverted to its preanginal configuration.

inferior ST elevation was present in two cases with right coronary artery spasm and was not seen with circumflex coronary artery spasm.

In one case spasm in the circumflex coronary artery was limited to a large marginal branch and ST segment elevation was limited to Leads V and V<sub>1</sub>.

ST segment elevation in Leads I, aV<sub>R</sub>, aV<sub>L</sub>, V<sub>1</sub>, or V<sub>2</sub> was not observed with spasm limited to the right coronary artery or to the circumflex coronary artery (although the number of observations involving the latter artery is admittedly small).

With severe spastic obstruction of the anterior descending coronary artery ST segment elevation was almost always seen in Lead I and V<sub>1</sub>. One exception was reported where ST elevation was limited to Lead I and V<sub>1</sub> and V<sub>2</sub>. Although with spasm of the circumflex coronary artery ST elevation was commonly also seen in Leads I, aV<sub>L</sub>, V<sub>1</sub>, and V<sub>2</sub>.

V<sub>3</sub> or V<sub>4</sub> these leads were not as sensitive for detection as were V<sub>1</sub> or V<sub>2</sub>. Moreover Leads V<sub>1</sub> and V<sub>2</sub> lacked specificity for anterior descending spasm.

ST segment elevation in Lead 2, 3 or aV<sub>F</sub> is a result of anterior descending spasm was not observed in these patients but has been reported to occur in some patients with extensions of the anterior descending artery around the apex into the inferior interventricular groove.

ST segment depression (presumably reciprocal to posteroinferior ST elevation) was common but not invariably seen in Leads I, aV<sub>L</sub>, V<sub>1</sub>, V<sub>2</sub> in cases of right or circumflex coronary artery spasm. Reciprocal ST depression, also seen in Leads V<sub>3</sub> and V<sub>4</sub> in some cases of right coronary artery spasm was uncommon in these patients. Leads with circumflex coronary artery spasm.

With anterior descending spasm if reciprocal ST segment depression was present, it was most likely to be seen in Leads 2, 3 or aV<sub>F</sub>, and rarely in Leads V<sub>3</sub> or V<sub>4</sub>.

Acute severe obstruction of two major coronary arteries due to simultaneous spasm of both vessels was occasionally seen. In one of three cases and in a case reported by Endo and associates,<sup>1</sup> combined involvement of the right and circumflex coronary arteries produced ST elevation in Leads I, 2, 3, aV<sub>R</sub>, and V<sub>1</sub>, and V<sub>2</sub>. The presence of ST elevation in Lead I has never been observed with isolated right coronary artery spasm so that these changes are quite characteristic of simultaneous involvement of the circumflex artery or of a dominant circumflex artery. Although one might assume that the absence of ST elevation in Leads V<sub>3</sub> to V<sub>6</sub> mitigates against simultaneous involvement of the anterior descending artery, this in fact cannot be ruled out. A case reported by Berman and co-workers<sup>2</sup> of simultaneous spasm of the anterior descending (distal to a major diagonal branch) and circumflex arteries was associated with ST elevation limited to Leads I, 2, 3, aV<sub>R</sub>, and V<sub>1</sub>.

Combined spasm of anterior descending and circumflex arteries in one other instance produced ST elevation in Leads 2, 3, aV<sub>R</sub>, V<sub>1</sub>, and V<sub>2</sub>. In another case it caused ST elevation in Leads V<sub>1</sub> to V<sub>4</sub> and in yet another case it was associated with ST elevation limited to Lead I.

Lead showing greatest ST segment elevation

Table II Lead distribution of greatest ST segment shift in patients with variant angina

ECG lead	Inferior or inferolateral ST elevation (n = 67)			Anterior or anterolateral ST elevations (n = 38)		
	% of cases showing	% of cases showing	% of cases showing	% of cases showing	% of cases showing	% of cases showing
	Greatest ST elevation in this lead	Greatest ST depression in this lead <sup>a</sup>	No ST shift in this lead <sup>b</sup>	Greatest ST elevation in this lead	Greatest ST depression in this lead	No ST shift in this lead <sup>b</sup>
I	0	1	27	3	2	40
II	14	0	0	0	17	26
III	51	0	0	0	44	28
aV <sub>R</sub>	0	1	75	0	5	79
aV <sub>L</sub>	0	44	4	3	0	36
aV <sub>F</sub>	30	0	0	0	19	26
V <sub>1</sub>	2	0	37	0	0	28
V <sub>2</sub>	0	29	28	33	0	1
V <sub>3</sub>	1	14	30	45	0	1
V <sub>4</sub>	0	6	39	24	2	1
V <sub>5</sub>	0	1	40	0	1	32
V <sub>6</sub>	2	3	42	0	9	36

In cases where the greatest ST shift was equal in 2 or 3 leads, 1/3 credit was given to each lead respectively for that case. Total may not add up to exactly 100% because of rounding off to nearest whole number.

<sup>a</sup>Total adds up to more than 100% because more than one lead per case usually had a ST segment shift.

<sup>b</sup>Inferior ST elevation means ST level in Leads I and aV<sub>L</sub>. Inferolateral ST elevation means ST elevation in Leads II and aV<sub>L</sub> or aV<sub>F</sub>. Anterior ST elevation means ST elevation in Leads V<sub>1</sub>-V<sub>4</sub>. Anterolateral ST elevation means ST elevation in Leads V<sub>5</sub>-V<sub>6</sub> and concomitantly also in Leads V<sub>1</sub> and V<sub>2</sub> and/or I and aV<sub>L</sub>.

Table II shows the relative frequency with which the greatest amount of ST segment elevation was demonstrated in the 12 leads of the standard ECG during variant angina attacks in the 114 cases of group II.

With inferior or inferolateral ST segment elevation the degree of ST shift in Leads II and aV<sub>F</sub> in a given case was usually nearly equal. But where differences existed the greatest amount of ST elevation was usually present in Lead III and the least was present in Lead II. There were rare cases where the maximum ST segment elevation was seen in Lead V (two cases) or in V<sub>1</sub> (two cases).

With anterior or anterolateral ST segment elevation the greatest ST segment shift was usually seen in Lead V<sub>1</sub>, less frequently in Leads V<sub>2</sub> or V<sub>3</sub> and rarely in Lead I or aV<sub>L</sub>.

Maximal reciprocal ST segment depression in cases of inferior or inferolateral ST elevation was most frequently seen in Lead aV<sub>L</sub>, less commonly seen in Leads V<sub>5</sub> to V<sub>6</sub> and rarely seen in Lead I, aV<sub>R</sub>, V<sub>1</sub> or V<sub>2</sub>. With anterior or anterolateral ST segment elevation greatest reciprocal ST depression was usually seen in Lead III, less commonly

seen in Leads II, aV<sub>F</sub> or V<sub>6</sub> and rarely seen in Leads I, aV<sub>R</sub> or V<sub>1</sub>. The lead least likely to show any ST segment shift with either inferior or anterior ST elevation was aV<sub>R</sub>.

## Discussion

**Critique of methods.** Not insisting on recording of the multilead ECG demonstrating ST segment elevation simultaneously with the angiographically demonstrated coronary arterial spasm producing the variant angina attack allows criticism of this study on the ground that the location of spasm could move from one vessel to another from one attack to another and the vessel in spasm during the ECG recording might be different from the vessel seen to be in spasm at angiography. This type of criticism is also applicable to my inclusion of cases of coronary spasm induced by drugs. Any one having experience with large numbers of these patients knows how difficult it is to obtain a multilead ECG during an attack and how much more difficult it is to obtain a coronary arteriogram during an attack. One would think that it would be easy to obtain a multilead ECG lead during the presence of coro-

nary spasm during arteriography. In actual practice most angiographic laboratories are (unfortunately) set up to monitor only one ECG lead during arteriography. The attacks of spasm are evanescent and the gross changes in the ECG produced by selective coronary injection of contrast medium markedly reduce the time available to record the ECG alterations due to the spasm itself.<sup>10</sup> All this has conspired to produce a situation where actual multilead ECG recordings of variant angina attacks during coronary arterial spasm simultaneously documented angiographically are rare indeed.

Thus in order to obtain the relatively large number of observations to address the question in this study, compromises on that which is ideal have been made. That these compromises are reasonable is indicated by the fact that in my experience and that of others repeated attacks of variant angina usually involve the same coronary artery in a given patient. Although exceptions occur they are relatively rare: the reported incidence being between 5% and 15% of all variant angina cases.<sup>11,12</sup> Likewise variant angina attacks provoked by the ergonovine maleate almost always involve the same coronary artery distribution as the spontaneous attacks.<sup>13,14,15</sup>

This study does not deal with the problem of ST segment depression resulting from subendocardial ischemia produced by coronary artery spasm resulting in a lesser degree of obstruction than that required to cause ST segment elevation. There is probably no qualitative difference between the spasm causing ST depression and that causing ST elevation and both can occur in the same leads in the same patient during different phases of one attack of variant angina or during different attacks.<sup>1</sup>

**ST elevation and coronary spasm correlation.** It is of course not surprising that anterior descending coronary arterial spasm produces ST elevation in the anterior precordial leads and that right coronary artery spasm produces ST elevation in Leads 2, 3 and aV<sub>F</sub>. This is consistent with the results of ECG arteriographic correlations in patients with old transmural myocardial infarction.<sup>16</sup> The insensitivity of Leads V<sub>1</sub> and V<sub>2</sub> in showing ST elevation with acute anterior descending obstruction is not so well known however. These latter leads are also very nonspecific for localizing the coronary artery involved since they may show ST elevation with obstruction of any of

the three major coronary arteries. Also it is generally appreciated that Lead V<sub>1</sub> can show ST elevation in some cases of right coronary artery obstruction presumably due to anterior right ventricular ischemia. Also Lead V<sub>1</sub> is relatively insensitive in detection of ST shift due to anterior descending obstruction.

This is of clinical importance because even present leads equivalent to V<sub>1</sub> are commonly used as the single monitored lead for detecting rhythm disorders in the coronary care unit (CCU) or with Holter type monitoring and leads equivalent to V<sub>2</sub> or V<sub>3</sub> are similarly used as single leads to search for ischemic ST segment shift in CCU with Holter type monitoring and during exercise testing. These practices will result in missing many cases of transient ST elevation. Even if a caught ST elevation in these leads gives relatively little information about the coronary artery involved. If ST depression reciprocal to ST elevation elsewhere were seen in these leads, and interpreted as indicating subendocardial ischemia, the clinician would be misled about the location of the ischemic myocardium and perhaps even about the nature of the ischemic attacks.

It is also not widely appreciated that ST segment elevation in Leads 2, 3 and aV<sub>F</sub> does not unequivocally distinguish between obstruction of the right coronary artery and that of the circumflex coronary artery even in cases of right coronary artery dominance. The electrocardiogram during an attack does not allow such a distinction to be made unless there are additional findings, such as ST elevation in Lead V<sub>1</sub> (not seen in circumflex obstruction) or transient sinus or Hisian AV block when the source of the artery is the AV node is known. Spasm of the circumflex artery is thus one possible explanation for the failure to see obstruction develop in the right coronary artery during variant angina associated with inferior ST segment elevation. It is undoubtedly the great variability of the amount of posterior-inferior left ventricle supplied by the right and circumflex coronary arteries (with complete left coronary dominance at one extreme and marked right coronary dominance at the other) accounts for the ambiguity of ST elevation in Leads 2, 3 and aV<sub>F</sub>.<sup>17</sup>

The presence of ST elevation simultaneously in Leads 2, 3 and aV<sub>F</sub> and anterior precordial Leads V<sub>1</sub> to V<sub>4</sub> suggests spasm involving two arteries.

interior descending with either circumflex or right coronary artery) or possibly the left main coronary artery. Also ST elevation in Lead 1 along with that in Leads 3 and  $aV_L$  indicates involvement of at least some part of the left coronary artery system."

"Even a full standard 12 lead ECG will fail to show any ischemic ST segment shifts on occasion during complete spastic occlusion of a major coronary artery. In some cases this may be because there was no ischemia produced" "due to an alternate source of blood to that distribution such as from a collateral circulation not detected at angiography or perfusion of the distal end by a bypass graft"<sup>10</sup> In other cases angina could be produced and ischemia be present in an area of the left ventricle not well covered by the standard ECG (specifically high posterior left ventricular wall ischemia due to obstruction of the circumflex artery<sup>7</sup>)

"Selection of leads to monitor. It can be seen from the foregoing that no single ECG lead will suffice to detect all possible episodes of ST segment elevation due to coronary artery spasm. The more leads that are used the more sensitive will be the detection system. But there are practical constraints. In many places there is facility or only single lead monitoring.

For detecting ST elevation due to spastic obstruction of the anterior descending coronary artery. Lead  $V_1$  combines the advantages of greatest sensitivity, specificity and degree of ST segment change. Lead V runs a close second. For detecting inferior ST segment elevation due to spastic obstruction of either the right coronary artery or circumflex coronary artery. Leads 3 and  $aV_L$  are almost equally good, with Lead 3 having a slight advantage in showing a greater magnitude of ST shift.

Of 339 cases of variant angina gathered from my own series and from the world literature in whom Leads 3 and  $V_1$  were recorded during an attack having ST elevation in some lead the ST elevation was documented in either Lead 3 or  $V_1$  (or rarely both) in 333 cases (98.2%). Of the remaining six cases primarily involving localized lateral ST elevation the ST elevation would have been detected in five by the addition of Lead  $aV_L$  and in three by the addition of Lead V.

Thus if one can monitor only one lead and there is no clue as to where the ST elevation will

appear (such as T wave inversions between attacks or known single vessel coronary stenosis) then Lead 3 is a reasonable choice since inferior ST elevation is slightly more common in variant angina than anterior ST elevation. If two leads can be monitored Leads 3 and  $V_1$  will assure an excellent chance of detecting any ST elevation. If three leads can be observed simultaneously Lead  $aV_L$  could be added although I prefer to use  $V_1$  or V instead for exercise or pacing tests since what sensitivity is lost in picking up ST elevation is more than made up for by the increased sensitivity of these latter leads in detecting ischemic ST segment depression of subendocardial ischemia.

### Summary

The lead distribution of ST segment elevation produced by severe spasm of major coronary arteries was correlated with the specific artery involved in a group of 110 cases of variant angina with single vessel coronary arterial spasm made up from eight cases personally observed and 102 cases abstracted from published literature.

The most sensitive and specific lead for ST elevation during anterior descending (LAD) coronary arterial spasm was  $V_1$ . V was almost as good. For spasm of either the right (RCA) or circumflex coronary artery (CMFX) Leads 3 and  $aV_L$  showed ST elevation most frequently. Electrocardiographically it was difficult to distinguish between spasm of these two vessels. ST elevation in Leads V and  $V_1$  was not specific occurring in some cases of spasm of each of the three major coronary arteries. ST elevation in Lead  $V_1$  occurred in either RCA or LAD spasm but never in CMFX spasm. ST elevation in Lead 1 was never seen with isolated RCA spasm.

No single lead can detect all cases of transient ST elevation. Simultaneous monitoring of Leads 3 and  $V_1$  would have detected 98.2% of 333 cases of ST elevation reviewed and addition of Lead  $aV_L$  would have detected most of the remainder. These findings should be considered in lead selection for monitoring to detect ST elevation and in using the ECG to identify spastic coronary arteries.

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# Prognostic significance of an ST segment depression of patients with an acute coronary attack

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An ST segment elevation as an indicator of myocardial injury is well known. Several studies based on the 12 lead ECG or on surface mapping deal with this ECG pattern. On the other hand the opposite pattern, an ST segment depression, has stirred little interest among researchers excluding studies on exercise stress ECG.

A depressed ST segment has traditionally been connected with a subendocardial myocardial infarction (MI) or regarded as a reciprocal sign of an ST segment elevation in the opposite leads.<sup>1</sup> In an earlier autopsy study we showed that an ST segment depression of a definite shape and depth in an ECG taken shortly before death was found in 88% of patients with an acute circumferential subendocardial MI and in 43% of those with a regional subendocardial MI or a transmural MI. An ECG taken at admission may even indicate the prognosis of a patient with an acute MI. ST segment depression was found in half of the patients who died within three weeks.<sup>2</sup>

The shape of the ST segment depression as well as its depth are usually well defined in studies on exercise stress ECG, but we have found only a few studies dealing with the conventional ECG that give exact definitions of the shape of

the segment and of the depth of the depression.<sup>3-5</sup> Since a specific type of the ST segment depression seems to occur frequently in patients with various types of acute MIs leading to death, further studies on this ECG pattern in patients with an acute attack of chest pain seem necessary.

## Material and methods

The original series consisted of 636 patients (424 men and 212 women) admitted to the Kuopio University Central Hospital during a period of 14 months because of an acute attack of chest pain lasting at least 20 minutes. Patients whose attack was considered of extracardiac origin were not included in the series, nor were patients who died before the first day ECG recording (14 patients) nor were those with a right or left bundle branch block or a ventricular rhythm, including patients with artificial pacemakers. The material of this analysis was thus composed of a total of 580 patients, 386 men and 194 women. The age of the men ranged from 28 to 89 years with a mean of 59 years and of the women from 37 to 86 years with a mean of 65 years.

**Electrocardiography** The ECGs were recorded with an ink jet recorder with a frequency response of 0 to 700 cycles per second (Olli 326 Kone Instruments, Helsinki, Finland).

The electrocardiograms were analyzed by an experienced reader. The ECGs included in the study were recorded at the following phases in

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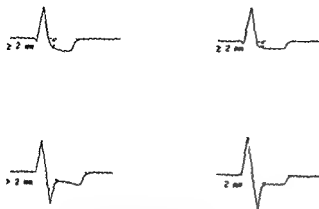


Fig 1 Various manifestations of definite ST segment depression. The interval between the arrows is 2 mm (0.2 mV) or more.

the morning of the first and the third day after admission at the end of the hospitalization period 6 weeks, 16 and 12 months after admission.

**ST segment depression.** The J point depression was measured in millimetres with the PQ segment as the reference line. Only cases with the J point followed by a horizontal or a downward sloping ST segment lasting at least 0.08 sec were noted. Thus cases with a so called junctional ST segment depression showing an upward going ST segment were not included. The depression of the isoelectrical line caused by an atrial T wave was noted and its depressing effect on the J point was eliminated.

The ST segment depression was regarded as definite if the J point was depressed 2 mm or more at least in one lead and if it was followed by the above mentioned shape of the ST segment (Fig 1).

The QRS criteria of an MI and those of an ST segment elevation in a myocardial injury are presented in our earlier paper. Left ventricular hypertrophy (LVH) was considered to be present if the height of the R wave in Leads V<sub>1</sub> or V<sub>4</sub> was 26 mm or more or in any of the Leads I, II, III or aV<sub>1</sub>, 20 mm or more or in lead aV<sub>1</sub>, 12 mm or more or if the sum of the height of the R wave in Lead V<sub>1</sub> or V<sub>4</sub> and the depth of the S wave in Lead V<sub>1</sub> was 35 mm or more.

In the study the following leads were grouped as follows:

- Leads I, aV<sub>1</sub>, V<sub>1</sub> as the lateral lead set
- Leads II, III, aV<sub>1</sub> as the inferior lead set
- Leads V<sub>1</sub>, V<sub>2</sub> as the anterior lead set
- Leads V<sub>2</sub>, V<sub>4</sub>, V<sub>5</sub> as the anterolateral lead set

**Clinical data.** The heart rate was measured from the first day ECGs. The occurrence of the pain during the first days of hospitalization was recorded according to the study plan. The criteria used for a cardiogenic shock were the following: systolic blood pressure below 100 mm Hg, urinary secretion below 40 ml/minute, vasodilation in the periphery and signs of confusion.

**Laboratory diagnostics.** In the serum enzyme diagnostics of an acute MI the upper normal limit used for serum aspartate aminotransferase (ASAT or GOT) was 40 U/L + 3°C and for serum creatine phosphokinase (CK) 900 U/L + 37°C. In addition the serum enzyme curve was to show typical abnormal changes before was considered indicative of an acute MI. The lower normal limit of serum potassium was 3.9 mmol/L.

**Chest x ray study.** The chest x rays were from supine patients in the mornings of the first three days of hospitalization. The radiographs were analyzed by a cardiologist. The classification of pulmonary congestion into four grades was performed according to the method of Turndorf and associates.<sup>6</sup> The heart size was estimated by the C/T ratio where C is the sum of the maximum distances of the right and left border of the heart from the medial line and T the maximum width of the osseous chest at the level of the heart-diaphragmatic angle.

**Division of the patients into groups according to the diagnostic criteria.** The patients were divided into the following groups:

**Group A.** Patients with typical chest pain, serum enzyme changes indicative of a recent MI or patients with autopsy evidence of an acute MI (263 men and 110 women).

**Group B.** Patients with a typical chest attack but no significant changes in the serum enzyme levels (49 men and 50 women). In cases QRS signs of an MI were present. In remaining cases either an ST segment elevation of injury or an ST segment depression of 1 mm or more was found if the depression developed in the acute phase and disappeared after days.

**Group C.** Patients with a typical chest attack but no serum enzyme reactions indicative of an acute MI (74 men and 34 women). Changes which did not fulfill the criteria of Group B were found in the ECGs of these patients.

**Follow up.** Follow up examinations of

able 1 Prevalence of an ST segment depression in the ECGs taken during the first three days of hospitalization in the material of 386 men and 194 women admitted to hospital because of a heart attack

Lead sets	Depression of J point in millimeters								Total number of cases	Per cent	
	Definite ST segment depression										
	1-1.9	2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7 mm or more				
<b>Men</b>											
I aV V	23	13	3	1				17	4.4	40	10.4
II III aV	7	6						6	1.6	13	3.4
V V	8	10	11	2	3	2	1	24	6.2	39	8.3
V V V	37	26	11	5	4	11	4	52	13.4	89	23.1
Any of the lead sets	47	40	11	6	5	3	4	69	17.9	116	30.1
<b>Women</b>											
I aV V	29	19	1		1			14	7.2	43	22.2
II III aV	17	3	11					5	2.6	23	11.3
V V	11	7	2					9	4.6	38	19.6
V V V	25	28	7	4	2			41	21.1	66	34.0
Any of the lead sets	37	29	10	6	1			46	23.7	78	40.2

patients were performed after 6 weeks 3 6 and 12 months after admission Two hundred seventy nine men and 139 women attended the last follow up examination

One hundred eighteen patients (81 men and 37 women) died during the follow up year The mortality rate in Group A was 27.3% in Group B it was 13.1% and in Group C it was 2.8% A coronary heart disease was considered to be the basic cause of death of all but four persons in Group A of all in Group B and of all but one in Group C The four patients in Group A had a severe respiratory infection and the patient in Group C had an acute cerebral hemorrhage

## Results

Prevalence of an ST segment depression A J point depression of 1 mm or more followed by a horizontal or downward sloping ST segment in any of the four lead sets was found in 30% of the male and in 40% of the female patients admitted to hospital because of an acute coronary attack (Table I) The depression was most frequent in the anterolateral lead set (Leads V<sub>1</sub> V and V<sub>2</sub> Table I) Fifty eight men (15%) and 91 women (91%) had a depressed ST segment in two or more of the lead sets

A definite ST segment depression (the J point

depression 2 mm or more) was found in any of the lead sets in 69 men (17.9%) and 46 women (23.7%) (Table I) The age of these men ranged from 36 to 89 years with the mean of 63 years and of the women from 56 to 85 years with the mean of 69 years The age of the remaining 317 men without a definite ST segment depression ranged from 28 to 86 years (mean 58 years) and of the 148 women from 37 to 86 years (mean 64 years) The patients with a definite ST segment depression thus were older than patients without this pattern ( $p < 0.01$ )

**Correlation between the definite ST segment depression and an acute MI** In 63 out of the 69 men and in 36 out of the 46 women with a definite ST segment depression the serum enzyme curve indicated an acute MI (Table II) Five of the six men and three of the ten women without enzyme reactions had had an old MI

The definite ST segment depression was only infrequently found in leads with QRS signs of MI or in the leads opposite to the leads showing Q waves of infarction Most frequently the pattern was associated with QRS signs of an inferior MI and was most commonly seen in Leads V<sub>1</sub> V or V<sub>2</sub> There were 39 patients in whom no QRS signs of an MI but a definite ST segment depression was seen (Table III) In 28 of them (71%) serum

Table II Distribution of the patients with a definite ST segment depression into three groups according to the reliability of the MI diagnosis\*

	Men			Women		
	Total number of patients	Number of patients with a definite ST segment depression	Per cent	Total number of patients	Number of patients with a definite ST segment depression	Per cent
Group A	263	63	24.0	110	36	32.7
Group B	49	2	4.1	50	8	16.0
Group C	74	4	5.4	34	9	26.5
Total	386	69	17.9	194	46	23.7

A detailed definition of the groups is given in the section Material and methods

Table III QRS signs of an MI in the 115 patients with a definite ST segment depression figures indicate the number of patients

Leads with a definite ST segment depression	QRS sign. of an MI in leads				No QRS signs of an MI (39 cases)	Total number of cases with definite ST segment depression (115 cases)	
	I aV <sub>L</sub> V (17 cases)	II III aV <sub>F</sub> (45 cases)	V V (4 cases)	V <sub>1</sub> V <sub>2</sub> V <sub>3</sub> (10 cases)		No	%
I aV <sub>L</sub> V	—	6	—	1	1	8	7.0
II III aV <sub>F</sub>	2	—	1	3	—	6	5.2
V V	1	4	—	—	2	7	6.1
V V V	14	3	3	6	36	94	81.9

Table IV ST segment elevation in patients with a definite ST segment depression figures indicate the number of patients

Leads with a definite ST segment depression	ST segment elevation in the given leads				No ST segment elevation (78 cases)	Total number of cases with a definite ST segment depression (115 cases)
	I aV <sub>L</sub> V (4 cases)	II III aV <sub>F</sub> (25 cases)	V V (5 cases)	V <sub>1</sub> V <sub>2</sub> V <sub>3</sub> (3 cases)		
I aV <sub>L</sub> V	—	4	1	—	3	8
II III aV <sub>F</sub>	2	—	2	2	—	6
V V	—	4	—	—	3	7
V V V	2	17	2	1	72	84

enzyme reactions indicated acute MI. In these cases the definite ST segment depression was also most frequently found in one or more of the Leads V<sub>1</sub>, V<sub>2</sub> and V<sub>3</sub>. The ST segment was elevated in 37 out of the 115 patients with a definite ST segment depression (Table IV). The elevation was most frequent in the inferior lead set while the definite ST segment depression of these patients most commonly occurred in the antero-lateral leads. In 78 patients a definite ST segment depression but no ST elevation was evident (Table IV). Sixty five of them belonged to Group A.

The definite ST segment depressions in the recordings on the first three days appeared. In 12 patients the depression was found in the ECG taken at the end of hospitalization period. In the ECGs taken in follow-up studies the definite ST segment depression was found in 16 patients who had the pattern in the first day ECGs. It was found in the ECG of nine patients in first-day ECGs; this pattern was not seen.

Clinical correlations of the definite ST segment depression. The mean heart rate in patients with a definite ST segment depression was

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Table V Differences in certain clinical data between patients with and those without a definite ST segment depression in the ECGs recorded during the first three days of hospitalization

	Patients with a definite ST segment depression (total 115)			Patients without a definite ST segment depression (total 465)			Statistical significance
	Data available	Number of patients	Per cent	Data available	Number of patients	Per cent	
CG signs of left ventricular hypertrophy	115	49	42.6	465	116	24.9	$p < 0.005$
Pulmonary congestion of Grade 3 or 4 in the first three days x ray study	106	51	48.1	441	173	27.9	$p < 0.01$
C/T ratio 0.6 or more	103	36	35.0	387	85	22.1	$p < 0.05$
Low serum potassium level in the first day	94	19	20.2	280	56	20.0	$p = \text{n.s.}$
Severe chest pain during the first day	107	40	37.4	440	150	34.1	$p = \text{n.s.}$
Occurrence of cardiogenic shock during the first day	114	7	6.1	460	14	3.0	$p = \text{n.s.}$
Use of digitalis before admission	115	68	59.1	457	190	41.6	$p < 0.05$
Use of digitalis at the time of the one year follow up study	68	61	89.7	366	218	59.6	$p < 0.05$

minute (SD 27.4) and of women 91/minute (SD 7). The mean heart rate of men without the pattern was 83/minute (SD 24.3) and of women 89/minute (SD 23.9).

Electrocardiographic LVH was significantly more common in the ECGs of patients with a definite ST segment depression than in ECGs of patients without the pattern (Table V). Further more pulmonary congestion Grade 3 or 4 and a C/T ratio of 0.6 or more in any of the first three day examinations were more frequent in patients with a definite ST segment depression than in those without this pattern (Table V). There was also a significant difference between these patients in the prevalence of digitalis treatment both before admission and one year after admission (Table V). On the other hand there was no significant difference in the low serum potassium levels in the occurrence of persisting chest pain during hospitalization or in the occurrence of cardiogenic shock.

Mortality rate of patients with an ST segment depression. Within one year the mortality rate was lowest (14.2%) in patients with a J point depression less than 1 mm or no depression (Table VI). Both in men and women the mortality rate grew gradually with an increasing J point depression (Table VI). The highest mortality rate was found in men with a J point depression of 3 mm or more (55%). The one year mortality rate

of men with a definite ST segment depression was 48% and of women it was 30%. The one year mortality rate was also high in cases where the definite ST segment depression occurred in two or more lead sets, i.e. 19 of 30 men (54%) and six of 20 women (30%) died.

The difference in the mortality rate between patients with and without the definite ST segment depression developed during the first four weeks (Fig. 2). There was a significant difference in the mortality rate between these two groups during the first three days as well as during the first four weeks. After four weeks the increase of the mortality rate was the same in both groups (Fig. 2).

#### Discussion

The ST segment depression as defined in this study is rather a common ECG sign of coronary patients with an acute attack of chest pain. In our series the prevalence was 19.8%. When this ECG pattern occurs it seems to be of important clinical and prognostic significance. During the hospitalization period evidence of an acute myocardial infarction (AMI) was found in up to 86% of the patients with this pattern observed during the first three days succeeding admission. The pattern was frequent (14%) also in cases of AMI without conventional ECG signs of myocardial involvement. After the acute phase the pat-

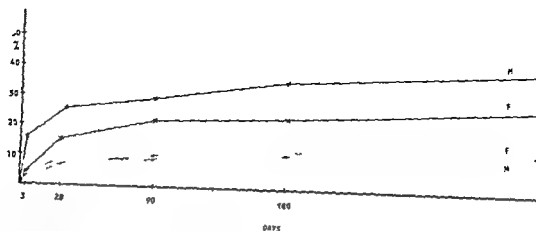


Fig 2 Cumulative graphs showing the mortality rates of patients with a definite ST segment depression and of those without the pattern (---). The exact time of death of four men and one woman with the pattern of four men and two women without the pattern was not known.

Table VI The mortality rate during the year after admission of the patients with varying degrees of a J point depression with a horizontal or downward sloping ST segment

	Men			Women			Total	
	Number of patients	Number of deaths	Per cent	Number of patients	Number of deaths	Per cent	Number of patients	Number of deaths
Less than one mm. or no ST depression	270	40	14.8	116	15	12.9	386	55
One mm. or more but less than 2 mm.	47	8	17.0	32	8	25.0	79	16
Definite ST segment depression								
Two mm. or more but less than 3 mm.	40	17	42.5	29	8	27.6	69	25
Three mm. or more but less than 4 mm.	11	6	54.5	10	5	50.0	21	11
Four mm. or more	18	10	55.6	7	1	14.3	25	11
Total	386	81	21.0	194	37	19.1	580	118

tended to disappear being less frequent at the end of the hospitalization period. After hospitalization the prevalence of the pattern was only slightly higher than that detected in population studies on middle aged Finnish people. The high hospital mortality rate of patients with this ECG pattern naturally had a selective effect on the composition of the follow up material.

Theories on the mechanism of the ST segment depression in AMI patients are rather controversial. A pronounced shift of the J point in the ECG is regarded as an essential feature in patients with a myocardial injury. Myers and colleagues demonstrated this already in 1951. Later experimental studies of Vincent and co-workers have

shown that a TQ segment (isoelectric displacement due to the loss of resting potential) is the major event resulting in ST segment displacement (secondary changes) in cases of myocardial injury. It is clear that in these cases the J point must be changed in proportion as the ST segment. In the ECG this has been demonstrated in ST depressions if the injury is subendocardial: the same type of ST segment depression is a frequent finding particularly in the first 24 hours with circumferential subendocardial MI in earlier series.<sup>4</sup> On the other hand action potential waveform changes (primary changes) are responsible for changes in the ST segment.

however has a lesser role in cases of myocardial injury while in association with tachycardia and digitalis effect it is the major cause of ST segment changes.<sup>11-13</sup> In cases of tachycardia or digitalis treatment the primary waveform changes cause shortening of the ventricular action potential with a steep slope of repolarization in phase 2.<sup>14-16</sup> The latter part of the ST segment then is deformed and often leads to a transmural type of ST segment depression. In order to decrease difficulties in the interpretation and as its significance seems to be controversial we have not included the cases with the so called junctional ST segment depression (depressed J point followed by an upward going ST segment).

According to present understanding many transmural infarcts if not all are initially subendocardial and only secondarily become transmural. Development of the myocardial injury to its total extent may last for hours or days. A clearly necrotic center of an AMI particularly at the initial stage is surrounded by rather an extensive zone of severe ischemia liable to progress into injury. This ischemic zone may be reflected as an ischemic ST segment depression in the ECG. Progression of this critical zone into injury worsens the prognosis of the patient. The high rate of mortality of AMI patients with an ST segment depression as well as the extensive acute myocardial lesions frequently revealed in fatal cases at autopsy suggest that the ischemic zone could be one explanation for the occurrence of this ECG pattern at the initial stage of an AMI. The concept of an ischemic zone is also supported by our frequent findings of an ST segment depression in leads adjacent to leads with signs of an AMI. The ST segment depression though possibly merely ischemic may if prolonged and if associated with significant changes in the enzymes represent subendocardial infarction circumferential or segmental but it may also relate to transmural infarctions. Although the QRS signs of an MI were most frequently found in the inferior lead set in our patients we cannot connect a definite ST segment depression solely with an inferior wall myocardial infarction. Possible changes associated with an anterior wall infarction may not have been detected because of the limited capacity of the 12 lead ECG to reflect the cardiac potential.

Some researches emphasize the role of metabolic ionic or hemodynamic alterations as the

basic cause of an ST segment depression.<sup>17-19</sup> This is supported by our unpublished results from an autopsy series of hospital deaths in which a definite ST segment depression was found in the ECG preceding death in some patients without coronary heart disease or a myocardial injury.<sup>14</sup> LVH associated with myocardial fibrosis as well as an acute collapse due to various causes seem to be frequent findings in such cases.

On the other hand there is certain evidence suggesting that an ST segment depression in an AMI is not caused by a myocardial injury. Experimental studies have shown that an ST depression can originate from well perfused areas surrounding the injury.<sup>20-22</sup> Furthermore samples taken from myocardial segments producing an ST segment depression have shown that the CK enzyme is not released from such areas.<sup>23</sup>

The ST segment depression in patients with an AMI can of course be reciprocal to the ST segment elevation of an injury. However it is obvious that in the ischemic conditions there are ST segment depressions caused also by other mechanisms.<sup>17-19</sup> This has also been proved experimentally.

1 An ST segment depression frequently occurs near the periphery of an injured area.<sup>3, 17, 19</sup>

2 An ST segment depression does not occur simultaneously with a maximum ST segment elevation.<sup>3, 23</sup>

3 An ST segment depression is evanescent while an elevation tends to be more stable.<sup>3, 23</sup>

4 In simultaneous recordings of the subendocardial and epicardial leads no relationship between the ST segment changes have been observed.<sup>3</sup>

In this study the ECG signs of LVH as well as the use of digitalis were more frequent in patients with a definite ST segment depression than in those without the pattern. Both LVH and digitalis therapy can of course make more pronounced the depth of the ST segment. On the other hand treatment with digitalis and LVH in the ECG are indicators of a severe heart disease. Enlargement of the heart and the frequent occurrence of pulmonary congestion in the early days of hospitalization in the x rays of patients with an ST-segment depression suggest a tendency to impaired functional performance of the heart. Furthermore the higher age of these patients may simply be related to the advancement of heart diseases with age.



Since the definite ST segment depression in an acute coronary attack seems to coincide with a severe degree of coronary heart disease, it is not surprising that during the one year follow up period the mortality rate of the patients with the depression in the acute phase was nearly three times as high as of the patients without the pattern. The difference in the mortality rate developed during the first four weeks after admission i.e. during the presence and healing period of the acute myocardial lesion. It must not pass unnoticed that the mortality rate increased along with a decreasing J point and with the number of lead sets showing the pattern. Clinical studies on exercise stress ECG have shown that the degree of ST segment depression in stress is related to the severity of coronary artery disease.<sup>21, 22</sup> Our results also support certain previous experiences gathered in the Coronary Drug Project,<sup>21</sup> although their definition of the ST segment depression slightly differed from ours.

### Summary

An ST segment depression was studied in the ECGs recorded on the first and third day after admission of 580 patients with an acute heart attack. An acute myocardial infarction was found in 86% of the 115 patients in whose ECG the J point was depressed 2 mm or more and the ST segment was horizontal or sloping downwards in at least one lead (a definite ST segment depression).

The degree of the J point depression was deemed of prognostic significance. During the first four weeks the mortality rate was lowest (4.7%) in patients with a J point depression less than one millimeter or no depression. The corresponding figure for patients with a definite ST segment depression was three times (21.7%) that of the patients without the pattern (7.3%).

The definite ST segment depression in an acute coronary attack seemed to be accompanied by a severe degree of coronary heart disease. Significant differences between the patients with a definite ST segment depression and those without the pattern were found in the C/T ratio in the degree of pulmonary congestion in the PCG signs of LVH and in the digitalis treatment.

It is concluded that the definite ST segment depression has an important clinical and prognostic significance in cases of acute coronary attacks.

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## Low dose heparin in the prevention of deep-vein thromboses in patients with acute myocardial infarction

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The radioactive fibrinogen test has been shown to accurately detect lower limb deep vein thrombosis.<sup>1-4</sup> Studies in patients with acute myocardial infarction using this technique have indicated an incidence of venous thrombosis of 29% to 38%.<sup>5-13</sup> Anticoagulants have been shown to significantly reduce the frequency of leg vein thrombosis and pulmonary embolism after acute myocardial infarction.<sup>1-11</sup> In postoperative patients where the incidence of deep vein thrombosis is of the same order as after myocardial infarction low doses of heparin have been shown to be as efficacious as full anticoagulation in decreasing the incidence of deep vein thrombosis<sup>12-14</sup> and fatal thromboembolism.

In a previous report from this department<sup>15</sup> the incidence of venous thrombosis in a fully anticoagulated group of patients with acute myocardial infarction was 9.4% and not significantly different from the 12.7% incidence in patients given 1 000 units of heparin by intravenous infusion daily for 48 hours. This report is of a second trial and presents the incidence of leg vein thrombosis in patients with myocardial infarction and compares a control group with two anticoagulant regimes: one using a low dose of intravenous heparin and the other full anticoagulation using heparin and warfarin sodium. The influence of cardiac failure in promoting venous thrombosis is also presented.

### Patients and methods

All patients with a myocardial infarction of less than 48 hours duration were considered for inclusion in the trial unless there was contraindication to anticoagulants where the patient was on anticoagulants or if cardiogenic shock was present since these patients were unlikely to survive the duration of the trial period.

One hundred and fifteen patients entered the trial and of these seven were withdrawn because of death before completion of the trial period three due to technical problems with the counting equipment and one because the attending physician requested a change in the anticoagulation regime. There were no instances of venous thrombosis or pulmonary embolism in the patients withdrawn from the trial.

Patients were randomized into one of two groups by the drawing of a sealed envelope. The fully anticoagulated group typically received 5 000 units of heparin intravenously as a bolus dose and then 20 000 units by intravenous infusion every 12 hours for 48 hours the dose adjusted to maintain a whole blood clotting time between 30 and 90 minutes. These patients were also given warfarin sodium on admission and the dose was continued after the cessation of heparin sufficient dosage to maintain the prothrombin index between 10% and 35%. A low dose heparin group were given 500 units of heparin in 5% dextrose by intravenous infusion every 12 hours for 48 hours. The control group received 5% dextrose by intravenous infusion for 48 hours. No anticoagulants were given to the last two groups after cessation of intravenous therapy.

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On admission to the coronary care unit patients were given sodium iodide intravenously followed by oral potassium iodide so as to block thyroid gland uptake of radioiodine. One hour after the administration of sodium iodide 200 microcuries of  $^{131}\text{I}$  labelled fibrinogen was given intravenously. Using a Pitman portable scintillation counter counts were made daily over the precordium and on eight sites on each leg for 7 to 10 days. The legs were elevated to 15 degrees for at least 15 minutes prior to counting. The leg counts were expressed as a percentage of the precordial count: a difference of more than 15% between adjacent sites on the calf or between identical positions on each leg was accepted as evidence of a venous thrombosis.

Patients were permitted to use a bedside commode but were otherwise confined to bed during the study period. All patients undertook active g and breathing exercises daily under the supervision of nursing staff. Daily examination was made of the legs to ascertain if clinical signs of venous thrombosis were present.

Patients were also assessed as to the presence or absence of cardiac failure which was diagnosed if there was a third heart sound, basal moist sounds, not clearing on coughing, or evidence of pulmonary venous congestion on a chest x ray which was taken daily for 3 days. Statistical analyses were made with the Fisher exact probability test.

# Results

Thirty seven patients were in the control group, 36 in the low dose heparin group and 35 in the fully anticoagulated group. The average age of patients in each group was similar. The control and fully anticoagulated groups showed a similar preponderance of males while there were only three females in the low dose heparin group. Mean admission time after infarction was slightly longer in the fully anticoagulated group. The mean SGOT was slightly lower in the control group compared with either treatment group (Table I). The groups were not significantly different when height, weight, body surface area or site of infarction as determined by ECG were compared.

The frequency of venous thrombosis (Table II) was 29.7% in the control group, 13.9% in the low dose heparin group and 11.4% in the fully anticoagulated group. The difference between either of the treatment groups when compared with the control group was significant ( $p < 0.05$ ) but

Table I

	Control	Low dose heparin	Fully anticoagulated
Mean age (years)	56.9	54.4	56.2
Sex M	30	33	27
F	7	3	8
Mean admission time (hours) after infarction	7.8	7.1	9.5
Mean SGOT	193	232	225

Retzman-Frankel units.

Table II

	No of patients	Venous thrombosis	% incidence
Control	37	11	29.7
Low dose heparin	36	5	13.9
Fully anticoagulated	35	4	11.4

there was no significant difference between treatment groups.

When divided according to the presence or absence of cardiac failure, there was a slight preponderance of patients with failure in the fully anticoagulated group compared with the control and low dose heparin patients (Table III). No significant differences were present in age or admission time after infarction. Patients with failure had higher mean peak SGOT levels compared with patients with no failure.

In the control group the patients with cardiac failure had a significantly higher incidence of venous thrombosis when compared to patients with no failure ( $p < 0.02$ ) (Table IV). In the low dose heparin group and in the fully anticoagulated group there was no significant difference between patients with and without cardiac failure. In patients without cardiac failure there was no significant difference between the control and either treatment groups. Conversely in patients with cardiac failure control patients had a significantly higher incidence of venous thrombosis when compared with the low dose heparin group ( $p < 0.05$ ) or the fully anticoagulated group ( $p < 0.02$ ) but the two treatment groups were not significantly different.

Of the 20 patients with venous thrombosis seven were persistent lasting 48 hours or more and 13 were transient. The right leg was involved in nine patients, the left in five and six were bilateral.

Table III

	Control		Low dose heparin		Fully anticoagulated	
	No CCF	CCF	No CCF	CCF	No CCF	CCF
No of patients	30	7	27	9	21	11
Mean (years)	56.6	57.4	53.3	57.8	55.7	55
Mean SGOT	196	225	205	311	18	24
Mean admission time (hours) after infarction	8.3	5.1	7.5	6.0	9.3	10

CCF = cardiac failure  
Reitman Frankel units

Table IV

	No of patients	Venous thrombosis	% incidence
Control	No CCF 30	6	20.0
	CCF 7	5	71.4
Low dose heparin	No CCF 27	4	14.8
	CCF 9	1	11.1
Fully anticoagulated	No CCF 21	3	14.3
	CCF 11	1	9.1

CCF = cardiac failure

eral. No trend was apparent in the persistence or otherwise of venous thrombosis in the different treatment groups. The time of diagnosis of the venous thrombosis varied between 1 and 8 days after admission the average being 4.5 days. Again no difference was apparent in the different groups. Venous thromboses were confined to below the knee and in no patient was the thrombus observed to extend above mid thigh. In only one patient was there clinical evidence of a venous thrombosis and no patient suffered a clinical pulmonary embolus.

## Discussion

The incidence of venous thrombosis of the legs in the control patients was 29.7% and is similar to the previously reported incidence of venous thrombosis in acute myocardial infarction and also in postoperative patients. Several reports have confirmed that anticoagulation reduces the frequency of venous thrombosis in patients with infarction from 38 to 55% using 40 000 units of heparin by intravenous infusion daily with oral anticoagulants from 29% to 0% using 40 000 units of heparin adjusted to maintain whole blood clotting time between 2½ and 3½ times normal.<sup>1</sup> The Medical Research Council reported a diminished frequency of thromboembolism in patients receiving full anticoagulation using heparin and phenindione compared

with a control group of low dosage phenindione but the diagnosis of events was made on clinical grounds only.

Low dosage heparin has been reported to reduce the incidence of venous thrombosis in postoperative patients when the labelled fibrinogen technique has been used to detect the complication. Using aqueous calcium heparin a dose of 5 000 units subcutaneously every 12 hours Kakkar and colleagues<sup>11</sup> demonstrated a reduction in incidence from 26% in controls to 4% in treated patients. Similarly Gordon Smith and colleagues<sup>12</sup> used 5 000 units of subcutaneous sodium heparin every 12 hours for three doses or 5 days and both groups had a lower incidence (13.3% vs 8.3%) of venous thrombosis compared with controls (42%). Nicolaidis and associates<sup>13</sup> used 5 000 units subcutaneously every 12 hours for 5 days and had an incidence of 0.8% compared with 10% in the control group. Gallus and co-workers<sup>14</sup> using 5 000 units of heparin subcutaneously 12 times daily reduced the incidence from 16.1% to 1.9% after elective surgery and from 48% to 1% after hip fracture.

We have previously reported a trial comparing two regimes of anticoagulants in affecting the incidence of venous thrombosis in patients with acute myocardial infarction. Low dose heparin (1 000 units daily) was not significantly different from a therapeutic regime of full heparin dose (controlled by whole blood clotting time) and warfarin sodium (controlled by prothrombin index) the incidence being 12.7% and 8.1% respectively. The present trial extends these results and confirms that a low dose heparin fully anticoagulated group have fewer venous thromboses than do control receiving no anticoagulants. In both trials the fully anticoagulated group showed a slightly lower incidence than the low dose heparin group but the differences were not statistically significant.

May 1971

When the results of the current trial are further examined to determine the difference in incidence of venous thrombosis in patients with and without cardiac failure there was inequality of numbers of patients in each group but those with cardiac failure on no therapy had a significantly higher incidence than did patients without failure. That patients with cardiac failure have a higher incidence of venous thrombosis is not surprising as it is well established that venous stasis is a predisposing cause of venous thrombosis.<sup>2</sup> In the two treatment groups statistical significance was not obtained when patients with and without failure were compared nor was there a difference in the three groups in patients without failure. Hence if these figures are confirmed by further trials anticoagulants have their major prophylactic role in patients with cardiac failure and very low dose heparin may confer the same benefit as full dosage of anticoagulants.

Previous reports in the literature have also shown that patients with cardiac failure have an increased frequency of venous thrombosis. Maurer and colleagues found a higher incidence of venous thrombosis in patients with a myocardial infarction complicated by left ventricular failure or cardiogenic shock compared with uncomplicated patients but the differences did not reach statistical significance. Miller and co-workers<sup>3</sup> in studying the effect of early ambulation on the incidence of venous thrombosis showed a significant increase in incidence in those patients with failure who were confined to bed. Kotilainen and associates found an increased incidence in patients with cardiac failure however this did not reach statistical significance if patients with cardiogenic shock were excluded. Cristal et al using a modified coronary prognostic index showed a significant difference in venous thrombosis when comparing patients in good clinical condition with those who were severely ill.

Handley<sup>4</sup> showed no difference in the incidence of deep vein thrombosis after myocardial infarction when 26 patients given low dose subcutaneous heparin were compared with 24 control patients. However the frequency of cardiac failure and the admission time after infarction were not indicated. The former as shown in this report is associated with a high incidence of venous thrombosis and if one group were weighted with a larger number of patients with failure and two groups may not be comparable. Further as Handley suggests low dose heparin prophylaxis may

not be effective if given some time after the event initiating the venous thrombosis but he does not state the admission time of his patients. In the present trial only patients with a myocardial infarct of less than 48 hours duration were accepted and the average admission time was less than 10 hours in each of our three groups. Kotilainen and colleagues used only oral anticoagulant therapy with warfarin sodium and as these may not be effective in preventing development of thrombi during the first 3 to 5 days these authors showed a relatively high incidence over all of 21%.

In the currently reported series patients were confined to bed (apart from use of a bedside commode) for the duration of the study. Miller and colleagues have demonstrated a significant reduction associated with early mobilization. The utilization of very low dosage heparin intravenously for the initial 48 hours together with early mobilization would seem to offer the greatest benefit with the least risk.

The labelled fibrinogen technique is only useful in the detection of calf vein and low thigh thrombosis and has little diagnostic capability for femoral vein thrombosis above mid thigh. There is evidence that thromboses limited to the calf have a lower risk of leading to pulmonary embolism.

Conversely there have been reports of pulmonary emboli in patients with thrombosis apparently confined to the calf.<sup>5</sup> In any case in a clinical study Sharnoff and de Blasio<sup>6</sup> reported a lower incidence of fatal thromboembolism in a group of operative patients receiving prophylactic heparin compared with controls.

The possible mode of action of low dose heparin remains speculative. There is evidence that heparin may potentiate the activity of a naturally occurring inhibitor to activated factor X.<sup>7,8,9</sup> Small doses of heparin may be adequate before tissue trauma activates factor X but if given later larger doses of heparin are required to reduce enhanced platelet stickiness that is observed following surgery,<sup>10</sup> and myocardial infarction.<sup>11</sup> O'Brien<sup>12</sup> has recently reviewed the possible modes of action of heparin in preventing venous thrombosis.

## Summary

Patients with acute myocardial infarction of less than 48 hours duration were randomized into three groups. The fully anticoagulated group received heparin by intravenous infusion and warfarin sodium.

um to maintain a whole blood clotting time of 30 to 90 minutes and a prothrombin index of 10% to 35%. The low dose heparin group received 500 units by intravenous infusion every 12 hours. The control group received no anticoagulants. The radioactive fibrinogen test was used to diagnose the presence of leg vein thromboses.

The control group had an incidence of venous thrombosis of 29.7% compared with 13.9% in the low dose group and 11.3% in the fully anticoagulated group. Patients in the control group who had cardiac failure had a significantly higher incidence of venous thromboses (71.4%) when compared with patients not in failure (20.0%). In the two treatment groups no significant difference was observed in patients with and without cardiac failure.

Patients with cardiac failure complicating an acute myocardial infarction have a high incidence of venous thromboses. Anticoagulants significantly reduce this incidence and low dose intravenous heparin is as efficacious as full anticoagulation.

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## Captopril in severe treatment-resistant hypertension

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True resistance of the blood pressure to conventional therapy is an uncommon but serious problem in the management of hypertensive patients. After factors such as poor patient compliance and excessive dietary sodium have been eliminated approximately 3 to 5% of patients are uncontrolled by various combinations of standard antihypertensive drugs. Studies in such patients suggest that a high peripheral vascular resistance persists despite drug therapy and may account for the blood pressure elevation. Moreover antihypertensive drugs may actually induce reactions such as fluid retention and elevated plasma renin activity that may raise blood pressure. Unfortunately even when effective these agents can produce undesired effects which limit their use. Captopril, an orally active angiotensin converting enzyme inhibitor is currently being investigated for the treatment of various forms of hypertension. It is believed to act primarily by blockade of the conversion of angiotensin I to angiotensin II although other mechanisms have been postulated. The purpose of the present study was to compare captopril alone or in combination with the highly effective regimen of diuretic propranolol and hydralazine in the treatment of resistant hypertension. Captopril in

combination with a diuretic or a diuretic and beta adrenergic blocking agent offered therapeutic advantages to the standard three drug regimen in a majority of our patients. In some patients however captopril's use was limited by side effects.

### Materials and methods

**Patients** To be eligible for the study a patient had to have a history of supine diastolic blood pressure (SDBP) exceeding 120 mm Hg and had to have failed on conventional drug therapy i.e. SDBP between 100 and 120 mm Hg or to have intolerable side effects from these agents. Men and women who fit these criteria gave written informed consent to participate in this study. Their mean age was 48 years with a range of 17 to 70 years.

An assessment of the etiology of the hypertension and the presence and degree of end organ involvement was made after a thorough history, physical and laboratory evaluation including renal scan or arteriography when indicated. The diagnosis of renovascular hypertension was based on the demonstration of significant stenosis of a renal artery associated with increased renal vein renin activity on one side or two to threefold increases peripherally. All patients were advised to follow moderate (75 to 100 mEq/day) sodium restriction throughout the study.

**Design of study** During a prerandomization period each patient was placed on standard triple therapy (STT) consisting of hydrochlorothiazide 100 mg/day or furosemide 80 to 120 mg/day, propranolol 320 mg/day and hydralazine 200

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Table 1 Characteristics and changes in blood pressure and heart rate of severely hypertensive patients before and after captopril (CAP) alone and in combination with diuretic (DIU) and propranolol (PPC)

Patient No	Age/Sex/ Race	Diagnosis/ End Organ Involvement	No of Drugs	Supine							
				Pre-STT		STT		CAP		CAP +	
				BP	HR	BP	HR	BP	HR	BP	F
<b>Group 1</b>											
1	34 FB	EH LVH Grade II	3	150/106	84	170/114	78	160/110	84	130/84	~
2	51 FB	RVH LVH stroke	5	210/112	68	198/168	68	172/116	90	112/75	~
3	58 MW	RVH CAD Grade I	5	212/114	56	210/118	75	190/106	78	200/86	~
4	40 FB	EH LVH Grade I	5	192/122	72	160/112	78	182/116	84	132/90	~
5	42 FB	RVH LVH RI Grade II	4	154/110	54	168/118	72	164/108	96	104/68	~
6	61 MW	RVH CAD RI Grade I	3	220/108	80	200/100	80	178/86	78	190/88	~
<b>Group 2</b>											
7	58 MW	RVH LVH Grade I	5	150/98	50	220/110	52	175/96	56	190/100	~
8	38 MW	MH IH LVH RI Grade IV	7	190/116	64	204/108	68	168/118	80	150/106	~
9	17 FW	EH RI Grade I	6	180/120	98	164/124	80	172/130	~	154/110	~
10	55 MB	EH LVH RI Grade II	5	260/110	78	240/112	72	170/104	88	174/108	~
11	30 MB	EH LVH RI Grade I	3	172/124	72	208/146	72	208/138	76	190/138	~
12	61 FB	EH LVH RI Grade III	3	230/150	76	212/112	72	230/112	68	180/108	~
13	63 MW	RVH LVH Grade I	3	240/140	64	220/120	60	194/120	80	198/108	~
14	50 MB	EH LVH Grade I	3	196/120	76	184/122	76	158/112	68	184/110	~
<b>Group 3</b>											
15	70 FB	EH LVH Grade II	3	242/114	68	220/120	68	212/128	120	230/118	~
16	41 MB	EH LVH RI Grade II	4	240/155	42	246/136	52	232/132	64	188/138	~

EH = essential hypertension MH = malignant hypertension RVH = hypertension associated with renal artery stenosis LVH = left ventricular hypertrophy RI = renal impairment (serum creatinine > 2.2 mg/dL) Grade I-IV = Keith Wagener Classification of retinopathy IH = intracerebral hemorrhage

Patient 10 never received metoprolol instead of propranolol.  
 Refer to text for drug doses and duration of each treatment.

mg/day. Two patients could not tolerate hydralazine because of previous lupus-like reactions. One took prazosin in place of hydralazine.

If after 2 to 3 weeks on this regimen a patient's SDBP remained between 100 and 120 mm Hg, he or she was admitted to the hospital and randomly assigned to either begin treatment with captopril or to continue STT for an additional period. For those assigned to captopril, it was initiated in a single dose of 25 mg and depending on response increased in a stepwise fashion to 150 mg. If SDBP did not decrease at least 10 mm Hg, the patient was considered an early treatment failure and was dropped from the study; otherwise, he or she was discharged for further follow-up. If the pressure was not controlled by captopril alone within a week, a diuretic was added after another 1 to 2 weeks. If the pressure remained uncontrolled for a week, a beta blocker was then added.

All patients who were randomized to continue

STT subsequently had uncontrolled blood pressure within 2 to 4 weeks after discharge. When this occurred, the STT was stopped and captopril was initiated. One patient with malignant hypertension and a SDBP > 120 mm Hg and a diastolic blood pressure > 145 mm Hg despite STT was randomized but was treated with captopril on an emergency basis.

After discharge, patients were seen every 3 to 4 days then weekly and then biweekly throughout the 3 months of the study. At each visit, supine and standing blood pressure and pulse rate were recorded and possible adverse effects were assessed. Pill counts and therapeutic medication dosage were made at each visit. New medication was dispensed. The study protocol was approved by the institution's Committee on Research.

Laboratory and safety assessment, including blood counts, urinalysis, and standard laboratory studies were done at specified intervals throughout the study.

Standing

AP + DIU + PROP*		Pre-STT		STT		CAP		CAP + DIU		CAP + DIU + PROP*	
BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR
		154/110	88	164/118	84	156/116	88	128/92	90		
		210/114	74	196/108	74	154/112	108	108/72	120		
		210/118	60	270/108	74	198/108	88	196/92	88		
		170/118	68	156/110	72	176/114	88	137/90	88		
		130/108	54	146/122	80	168/124	112	98/74	116		
		200/106	84	200/106	84	180/104	78	178/94	68		
168/90	60	138/88	52	212/112	56	160/96	52	180/104	84	138/80	60
122/85	82	170/106	68	198/134	68	168/118	84	147/104	102	110/86	98
150/92	84	140/90	92	130/105	92	182/140	—	156/118	104	146/90	94
168/94	52	190/110	80	200/120	74	168/118	80	175/122	86	140/90	52
136/92	64	180/130	76	200/150	72	194/142	76	158/120	110	133/98	74
178/106	76	220/145	80	200/110	76	218/110	68	186/100	72	164/98	98
160/106	64	230/136	64	220/124	64	174/128	68	189/118	72	170/100	56
134/90	58	194/128	68	174/120	92	176/118	72	148/108	88	140/96	72
220/120	76	234/110	72	248/130	72	200/114	64	200/112	124	240/118	72
230/124	60	240/150	60	230/124	64	240/138	72	187/136	78	200/120	68

At the study An electrocardiogram (ECG) was done before and during the study Careful ophthalmoscopic evaluation was performed at the beginning of the study and again after 3 months Plasma renin activity (PRA) was measured by radioimmunoassay<sup>11</sup> before starting captopril and subsequently after stabilization on a given regimen Normal values (mean  $\pm$  1 SD) on a 100 mEq Na diet are  $16 \pm 0.4$  ng/ml/hr

Statistical methods Blood pressures and heart rates used in the analysis represent the values obtained at the last visit before a protocol specified change in the treatment regimen Group means are presented with the standard error of the mean as the index of dispersion Student's *t* test for paired observations was used for analysis of the data A *p* value of less than 0.05 was considered significant

## Results

Patient characteristics Sixteen patients (nine men and seven women) aged 17 to 70 (mean 48 years) entered the study (Table I) Another woman with renovascular hypertension devel-

oped a skin rash after the first dose of captopril and could not complete the protocol her data are excluded Most had essential hypertension (EH) one (No 8) in the malignant stage The diagnosis of renovascular hypertension was made in three patients (No 5 and 6) and was strongly suspected in 3 others (No 2 and 13) on the basis of renal scan and PRA Fourteen of the patients had ECG evidence of left ventricular hypertrophy (LVH) Eight had significant renal impairment (serum creatinine  $> 2.4$  mg/dl) primarily due to nephrosclerosis in one patient (No 9) hemolytic uremic syndrome was the initiating cause of the renal insufficiency

Despite taking an average of four antihypertensive drugs (range 3 to 7) prior to entering the study the patients had unsatisfactory blood pressure control and in many cases side effects from the medications The mean SDBP on these drugs was  $207/120 \pm 12/5$  mm Hg while the supine heart rate (HR) was  $69 \pm 3$  beats/minute When placed on STT in the prerandomization period the mean SDBP was  $201/118 \pm 7/3$  mm Hg the HR on this regimen was  $70 \pm 3$  beats/minute

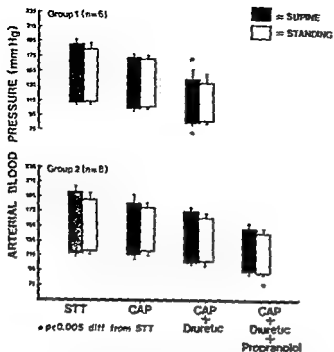


Fig 1. Supine and standing blood pressure responses to captopril (CAP) alone or in combination in hypertensive patients uncontrolled by standard triple therapy (STT = diuretic, propranolol and hydralazine). Refer to text for explanation of groups and doses.

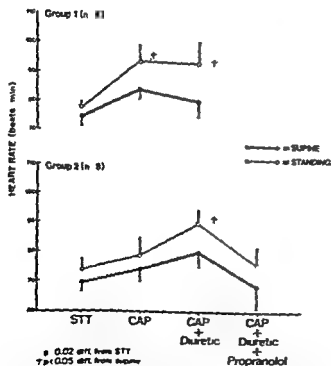


Fig 2. Supine and standing heart rate responses to captopril (CAP) alone or in combination compared to standard triple therapy (STT = diuretic, propranolol and hydralazine). Refer to text for groups and doses.

Mean PRA on STT just prior to starting captopril was  $98 \pm 21$  ng/ml/hr.

**Response to captopril** All 16 patients responded to captopril since even the patients who had failed to respond to STT eventually failed. In the hospital, after stopping STT, the SDBP was  $190/116 \pm 6/3$  mm Hg, the initial 20 mg captopril dose produced a mean maximal fall of  $36/19 \pm 5/3$  mm Hg. The response occurred at 15 minutes to 1 hour after drug administration and lasted 2 to 4 hours. The magnitude of the response was not enhanced by larger single doses (up to 150 mg) of captopril, but the duration of the blood pressure response was prolonged sometimes for as long as 6 hours. All patients had more than a 10 mm Hg fall in pressure but none became symptomatic.

As the effects of STT wore off, no patient could be controlled on captopril alone (up to 800 mg/day) and there was no correlation between initial and sustained blood pressure response. The sustained response to captopril for these patients averaged SDBP  $188/115 \pm 7/3$  mm Hg with a HR of  $80 \pm 4$  beats/minute. Since the blood pressure was not controlled on oral diuretics and if necessary, a beta adrenergic blocker was then added (see below).

**Group 1** Six of the 16 patients (Fig 1 top) controlled with captopril plus an oral diuretic, usually hydrochlorothiazide 50 to 100 mg daily. One patient (No 6) with reduced renal function later required furosemide in place of hydrochlorothiazide mainly to control edema. SDBP on this regimen was  $143/85 \pm 14/4$  mm Hg which was significantly less ( $p < 0.05$ ) than the blood pressure on STT and captopril alone. There was no significant difference between lying and standing blood pressures in this group for any treatment.

Supine HR (Fig 2 top) on captopril plus diuretic was not different from that on STT, however the standing HR on each of these two treatments was significantly ( $p < 0.05$ ) higher than that on STT. Likewise standing HR on these treatments was greater than supine HR ( $p < 0.02$ ) and in two patients (No 2 and 3) reached 108 beats/minute or higher.

PRA on captopril and diuretic was  $51 \pm 15$  ng/ml/hr compared to  $89 \pm 23$  ng/ml/hr on STT.

**Group 2** In another group of eight patients (Fig 1 bottom) the addition of propranolol was necessary to control blood pressure at home.

In this group captopril alone had produced a decrease in SDBP comparable to that of STT  $128/116 \pm 11/5$  mm Hg. Addition of hydrochlorothiazide or furosemide produced only a slight decrease in SDBP to  $175/111 \pm 6/4$  mm Hg. The addition of propranolol (40 to 80 mg/day) or metoprolol (150 mg/day) in one patient further reduced the SDBP to  $152/94 \pm 7/3$  mm Hg which was significantly different ( $p < 0.005$ ) from STT. There was no significant postural change in blood pressure for any treatment in this group.

Standing HR was higher during treatment with captopril ( $p < 0.05$ ) and diuretic than with STT ( $p < 0.02$ ). In addition a significant difference between supine and standing HR only occurred in the same regimen. Patients No 8 and 9 had HR increases to greater than 100 beats/minute and were symptomatic. Propranolol (40 mg/day) was effective in controlling both HR and symptoms in the latter two patients.

PRA on this regimen was  $38 \pm 14$  ng/ml/hr compared to  $11 \pm 3$  ng/ml/hr on STT.

**Group 3** The blood pressure of two patients (No 15 and 16) in spite of an initial good response to captopril alone could not be subsequently controlled by captopril, diuretic and propranolol at maximal doses. They were then classified as treatment failures even though SDBP decreased slightly from  $233/128$  mm Hg on STT to  $225/122$  mm Hg on this new regimen.

PRA for these two patients were 21 and 245 ng/ml/hr compared to 07 and 41 on STT.

**Adverse effects on captopril** Five of the original 17 patients developed a pruritic maculopapular skin rash. In one woman this occurred after the first dose and required stopping the drug. In the other patients it occurred after several weeks of captopril (mean dose 450 mg/day). In patients No 9 and 10 the rash resolved after 7 to 10 days in spite of the continuation of captopril although at a reduced dose. In patients No 11 and 8 a mild rash has persisted but has not required discontinuation of captopril. Patients No 7 and 10 also developed an abrupt loss of taste (ageusia) which lasted 2 weeks but spontaneously improved. ANA titers did not increase after captopril.

Two patients in Group 1 who had standing HR increases developed an acute myocardial infarction after 2 months of treatment. In patient No 2 use of propranolol to control heart rate was considered but she was asymptomatic and had

well controlled blood pressure. In patient No 8 propranolol could not be added because it had contributed to previous episodes of pulmonary edema more frequent angina responsive to nitrates preceded his myocardial infarction. Both these patients recovered without complications. Captopril was subsequently discontinued in patient No 2 as it was no longer needed to control her blood pressure.

Patient No 11 developed severe postural hypotension shortly after adding furosemide to captopril but this subsequently resolved. No other hemodynamic or laboratory abnormality was observed that could be attributed to captopril. Five patients had 2 to 3+ proteinuria at the beginning of the study; none of the others developed it while receiving captopril. Serum creatinine did not change in any group ( $p > 0.05$ ) and no changes were detected by slit lamp examination before and after treatment with captopril.

### Summary

The blood pressure of the majority of hypertensive patients can be controlled by sodium restriction and by one or at most two antihypertensive drugs. When the blood pressure does not respond a widely recommended three-drug regimen is an oral diuretic, propranolol and hydralazine.<sup>10</sup> Our 16 patients had essential and renovascular hypertension and were refractory to all previous therapy. The majority had end organ manifestations of severe hypertension such as left ventricular hypertrophy, renal impairment, retinopathy and neurologic sequelae. When they were placed on STT their blood pressure remained uncontrolled (SDBP  $> 100$  mm Hg). Because of the resistance of their blood pressure to STT all our patients were ultimately switched to captopril in an effort to achieve better control.

According to the protocol patients were hospitalized after stopping STT the night before. Captopril was started in a dose of 25 mg and increased according to the response. After the first dose no patient had a symptomatic hypotensive response though one patient's SDBP did fall 60/30 mm Hg. The maximum response to the initial dose usually occurred by 30 minutes, rapid for an oral medication. This initial response was often greater than the response to subsequent doses most likely due to the residual effects of STT. It is controversial as to whether the pretreatment PRA is a predictor of the response to

captopril.<sup>7-12</sup> In our study it was not possible to determine PRA uninfluenced by drugs on a controlled sodium intake because of the severity of the hypertension. PRA increased after captopril, a response consistent with interruption of negative feedback inhibition of renin release.<sup>11</sup>

As a group the patients' blood pressure on captopril alone approximated that on STT but no one was adequately controlled. The addition of a diuretic enhanced the effectiveness of captopril and in six of the 16 patients it resulted in satisfactory blood pressure control. Several of these patients who had hypertension in association with renal artery stenosis however manifested an upright tachycardia. Worsening of angina pectoris occurred in one man and he and another woman developed subendocardial myocardial infarctions; the role of the tachycardia in the precipitation of these events is unclear. Nonetheless diuretic induced volume depletion with blockade of the renin-angiotensin system by captopril may cause standing tachycardia, which may constitute a problem in patients with compromised coronary or cerebral circulation.

In this regard two of the eight patients in Group 2 though well controlled on captopril and diuretic had propranolol added in small doses (40 mg/day) to control symptomatic standing tachycardia. In the other six patients in this group blood pressure was normalized by this new three drug regimen and the regimen was well tolerated. Two patients (Group 3) could not be controlled even with this regimen and were considered treatment failures. It is of interest that propranolol produced additional blood pressure lowering in the presence of captopril which supports a hypotensive action of propranolol not due wholly to blockade of renin release.<sup>1</sup>

In general captopril was well tolerated; a number of patients remarked how much better they felt on captopril as compared to their previous regimens especially with regard to central side effects. Five patients manifested a maculopapular and pruritic rash but in only one did discontinuation of captopril prove necessary. In three patients the rash disappeared in 7 to 10 days with only a temporary reduction of captopril dosage. Two men developed a loss of taste which similarly resolved despite continuation of captopril. No other adverse effects have been noted in our patients. Renal function was maintained as serum creatinine did not change during the study.

Captopril induced proteinuria has been reported since the start of our study<sup>13</sup> but could not be documented retrospectively in our patients. However continued surveillance of captopril's effects especially proteinuria is necessary.

In summary, in our three month trial, captopril appears to provide a useful and important alternative for the management of severe refractory hypertension. Its mechanism of action seems to be ideal for such patients in whom the renin-angiotensin system appears to play an important role. Although alone it was insufficient to adequately control the blood pressure in our severely hypertensive patients its combination with a diuretic or a diuretic and a beta blocker often provided an effective and well tolerated combination. Nevertheless even with the latter three drug combination there were two treatment failures. Adverse effects such as skin rash, which occurred in 30% of our patients and loss of taste do not seem to seriously limit the use of the drug. The development of a sustained standing tachycardia when a diuretic is added to captopril may be harmful in some patients with a compromised cardiovascular system and requires careful consideration before treatment. Addition of low doses of beta adrenergic blocking agents if not contraindicated will control these heart rate increases. The benefits and hazards of long term captopril therapy in severe hypertension require further assessment.

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# The role of echocardiography in the selection of mitral valve prosthesis

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The problem of prosthesis patient mismatch after valve replacement has recently been highlighted with special reference to postoperative problems in patients with small valvular annuli<sup>1</sup>

Previous workers have stressed the occurrence of left ventricular outflow tract obstruction<sup>2,3</sup> and ventricular arrhythmias after mitral valve replacement with an unduly large prosthesis. Some investigators<sup>4</sup> demonstrated a markedly increased operative mortality rate in patients with narrow left ventricular outflow tracts who had received caged ball prostheses as compared to patients with left ventricular outflow tracts of similar dimensions who had received low profile prostheses.

This study attempts to analyze the relationships among the mitral valve prosthesis, left ventricular outflow tract dimensions and postoperative morbidity and mortality in a relatively large group of patients with pure or predominant mitral valve stenosis.

## Patients and methods

At the Mayo Clinic between January 1974 and January 1978 140 patients who had preoperative M mode echocardiograms underwent mitral valve replacement for pure or predominant mitral valve stenosis.

Seventy of these patients had M mode echocar-

diograms of sufficient quality to allow accurate measurement of the left ventricular outflow tract dimensions and this group forms the basis of this study. There were 56 females and 14 males and their ages ranged from 31 to 72 years, the average being 56 years. Patients with associated disease of other valves and clinically overt ischemic heart disease were excluded.

The preoperative M mode echocardiograms obtained routinely were analyzed by the measurement of the minimum diameter of the left ventricular outflow tract, as indicated by the shortest distance between the anterior mitral leaflet at the beginning of systole and the left side of the interventricular septum.<sup>5</sup>

The postoperative in hospital clinical course of each patient was studied by retrospective analysis of case records. Low cardiac output syndrome was diagnosed only if the patient exhibited persistent evidence of low systemic arterial blood pressure with signs of reduced peripheral perfusion and oliguria.

The surgical techniques employed were similar in all patients with hypothermia and aortic cross clamping being universally utilized.

The patients were placed into two main groups: group A were those (44 patients) with left ventricular outflow tract diameters in minimal dimension greater than 20 mm (normal dimensions) and group B were those (26 patients) with left ventricular outflow tracts less than 20 mm (small dimensions). The mean ages and bypass times of the two groups were comparable (Table I). There were 4 different types of prostheses used (Table II). The low cardiac output syndrome as previously defined and ventricular dysrhythmias occurred in both patient groups (Table III).

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Table I Patients undergoing mitral valve replacement

	Group A (44 pts)	Group B (26 pts)
Outflow tract diameter (mm)	>20	<20
Range	20 to 30	13 to 19
Mean age (yr)	56	55
Bypass time (min)		
Mean	57	62
Range	31 to 114	31 to 111

Table II Types of prostheses used for patients undergoing mitral valve replacement

Prosthesis	Group A	Group B	Total
Starr Edwards	10	13	26
Bjork Shiley	11	4	15
Braunwald-Cutter	10	9	23
Braunwald-Cutter	6	0	6
Total	44	26	70

Three categories were evaluated: patients with normal (> 20 mm) and narrow (< 20 mm) left ventricular outflow tracts who had received ball and cage prostheses (Starr Edwards) and patients with narrow outflow tracts who had received low profile prostheses (Bjork Shiley) (Table IV).

### Results and discussion

The overall operative mortality rate for the patients in this study (three of 70, 4%) was significantly lower than that observed in a previous report.<sup>3</sup> Since the patients in the latter report were operated on approximately 5 years before the present patient group, this difference may reflect significant improvements in anesthetic and surgical techniques that have occurred during this period.

The incidence of the low cardiac output syndrome was not significantly different in the patients with normal sized outflow tracts as compared to those with narrow outflow tracts or in the patients who received Starr Edwards prostheses in these two patient groups.

Thus we could find no evidence of an increased incidence of low cardiac output in patients with narrow outflow tracts who received ball and cage prostheses as has previously been noted.<sup>2,3,6</sup>

Table III Postoperative complications in patients undergoing mitral valve replacement

Complication	Group A (44 pts)	Group B (26 pts)
Ventricular dysrhythmia	8 (18%)	4 (15%)
Starr Edwards	5	2
Braunwald Cutter	2	0
Hancock	1	1
Bjork Shiley	0	1
Operative mortality	1 (2%)	2 (8%)
Low output syndrome	7 (16%)	6 (23%)
Bjork Shiley	3	1
Hancock	3	4
Braunwald Cutter	1	0
Starr Edwards	1	1
Mean cardiac index (L/min/M <sup>2</sup> )	1.4	1.7
Mean bypass time (min)	58	75

Table IV Patients undergoing mitral valve replacement

	Group A	Group B	
	Starr Edwards (13 pts)	Starr Edwards (13 pts)	Bjork Shiley (4 pts)
Bypass time (min)	46	55	71
Low output syndrome	1 (7%)	1 (7%)	1 (25%)
Ventricular dysrhythmias	5 (38%)	2 (15%)	1 (25%)
Operative mortality	0 (0%)	0 (0%)	1 (25%)

Only four patients with narrow outflow tracts received low profile prostheses (one patient developed a low cardiac output syndrome). Thus because of the few patients involved, this study does not allow a satisfactory answer to the question of whether the use of a low profile prosthesis would reduce the incidence of the low cardiac output syndrome.

Ventricular dysrhythmias were more frequent in the group of patients receiving ball and cage prostheses who had normal sized outflow tracts as compared to those who had narrow outflow tracts. This finding suggests that in these patients the possibility of mechanical irritation of the left ventricular myocardium producing



ventricular irritability was not a factor because this effect would be more likely to occur in patients with narrow outflow tracts. In this respect other mechanisms that contribute to ventricular ectopy such as hypoxemia, hypokalemia, acid base disturbances and mechanical stimulation by intracardiac lines<sup>7</sup> need to be considered.

Patients with normal and narrow outflow tracts who received Starr Edwards prostheses underwent similar surgical techniques (all had hypothermia and aortic cross clamping) and all had similar durations of bypass.

No patient receiving a Starr Edwards prosthesis died and thus we could not demonstrate any increased operative mortality in the group with narrow outflow tract who had received ball and cage prostheses—a finding that is distinctly different from that of previous studies.<sup>3</sup>

### Summary

Assessment of the left ventricular outflow tract was made echographically in 70 patients who subsequently received a mitral prosthesis. Group A (44 patients) had normal left ventricular outflow tract width ( $> 20$  mm); 13 received the Starr Edwards prosthesis and nine received the Braunwald Cutter prosthesis. There were two patients with low cardiac output syndrome and no hospital deaths. Group B (26 patients) had a

narrow left ventricular outflow tract ( $< 20$  mm). Thirteen patients received the Starr Edwards prosthesis. One patient had low cardiac output syndrome and there were no hospital deaths. We conclude that the use of the ball and cage prosthesis in the mitral position in patients with a narrow left ventricular outflow tract ( $< 20$  mm) measured echographically is not associated with an increased surgical risk.

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# Comparison of antiarrhythmic effects of oral prajmalium bitartrate and intravenous lidocaine in acute myocardial infarction

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Intravenous lidocaine is widely used in the treatment of ventricular arrhythmias in acute myocardial infarction.<sup>1-3</sup> Some authors favor its prophylactic use in all patients with myocardial infarction.<sup>4-12</sup> Prajmalium bitartrate is the salt of the quaternary ajmalium base isolated from *Sauwola serpentina* and has potent antiarrhythmic effects. The refractory period is increased and the conduction velocity is reduced. This is evident from an increased AH and HV intervals.<sup>8</sup>

Numerous studies document the antiarrhythmic effect of prajmalium bitartrate in patients with persistent ventricular arrhythmias.<sup>13-16</sup> An effect was also proved in patients with acute myocardial infarction compared to an untreated control group.<sup>3, 17</sup>

Administration of intravenous drugs is preferred in the treatment of arrhythmias in acute myocardial infarction. In the present study the effect of intravenously administered lidocaine and of orally administered prajmalium bitartrate was compared. The onset of effect of both drugs and their efficacy in the reduction of premature ventricular complexes and of runs of these complexes were quantitatively compared to the results in an untreated control group.

## Patients and methods

Thirty five patients with myocardial infarction were studied. The spontaneous frequency of premature ventricular contractions was registered during a 4 to 6 hour control period in which 7 to 250 ectopic beats per hour were counted. Patients with life threatening frequencies of premature ventricular contractions and runs of these complexes were not included in the protocol. These patients were immediately given lidocaine intravenously. The remaining patients were divided at random in control and treatment groups. In nine patients prajmalium bitartrate (Neo Gilurymal, Gulini Pharma, Hannover, West Germany) was administered orally and compared randomly to control patients. Then nine patients received lidocaine (Xylocaine, Astra Chemicals GmbH, Wedel/Holstein, West Germany) intravenously and were compared randomly to untreated patients. Thus a total of 17 patients had no antiarrhythmic therapy.

The patients of the control group had a mean age of 58 years. Nine of 17 patients had inferior and seven had anterior myocardial infarction. In one patient the area of infarction could not be localized. The infarction assessed according to the onset of pain occurred an average of 35 hours prior to the beginning of the control period. Patients treated with prajmalium bitartrate had a mean age of 60 years. Three of these patients had anterior and six had inferior myocardial infarction. Infarction occurred in the mean 57 hours prior to the control period. Patients treated with lidocaine (n = nine) had a mean age of 54 years. Four of these patients had anterior and five had

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## Frequency of PVC/h in the control period

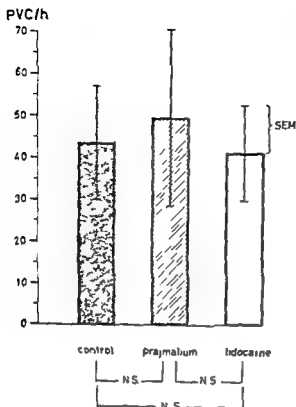


Fig 1 All patients received no antiarrhythmic treatment during a 4 to 6 hour control period. The frequency per hour of premature ventricular complexes (PVC/h) did not differ significantly. NS = not significant.

inferior myocardial infarction which occurred at the average 3.4 hours prior to the control period.

**Registration of arrhythmias** Premature ventricular contractions and runs of such complexes—defined as two to nine ventricular beats—were quantified from stored continuous electrocardiographic tape recordings (Meditape AR Siemens AG Erlangen W Germany) using a semiautomated arrhythmia detection system. This device registers all ectopic beats, missed beats, and all artifacts. All events are inscribed on a strip chart recorder together with the last two to three normal QRS complexes which are stored by a special device. The recordings were analyzed by hand every hour or every other hour. The heart rate and the frequency of arrhythmias detected with an incorporated automatic analyzer were monitored by a trend recorder.

**Protocol** After the control period nine patients received prajmalium bitartrate in three single

doses at 4 hour intervals (total dose 60 mg) and a subsequent drug free period of 18 hours. The total investigation period lasted 32 hours.

After the control period nine other patients received permanent infusions of lidocaine by means of an infusion pump (Perfusor Braun, West Germany). Patients received 2.1 mg/min corresponding to a total dose of 3000 mg over 4 hours. The total investigation period lasted 32 hours. Only in three patients was an initial bolus injection (100 mg intravenously in 3 minutes) of lidocaine administered. These three patients had premature ventricular contractions and numerous runs of such complexes which required an immediate bolus injection.

Frequency of premature ventricular contractions per hour and of runs of such complexes per hour were compared in all groups during antiarrhythmic treatment. The percent frequency was compared with that in the control period. Statistical analysis was done using Student's *t* test if unpaired comparison with a two-tailed error probability (2 p).

## Results

**Comparability of patient groups** The initial 4 to 6 hour control period prior to onset of treatment was necessary to establish comparable values in all three groups. In the control group 43 ± 14 (mean ± 1 standard deviation) premature ventricular complexes (PVC) per hour occurred. Patients treated with lidocaine had 41 ± 11 PVC/hr and those treated with prajmalium bitartrate had 49 ± 21 PVC/hr. Frequencies did not differ significantly (Fig 1 and Table I). Only initial values of runs of premature ventricular complexes differed however insignificantly (control group 2.2, lidocaine group 3.1 and prajmalium bitartrate group 6.9 runs/hr).

Patients in all groups had similar enzyme values (GOT, CK, and LDH). Peak creatine kinase values were similar in all three groups indicating a comparable extent of infarcted area. Serum potassium values were comparable in the control and in the lidocaine group. Only patients of the prajmalium bitartrate group had lower potassium values (Fig 2).

**Premature ventricular complexes** The frequency of premature ventricular complexes decreased under both drugs and also in the control group. Six hours after the administration

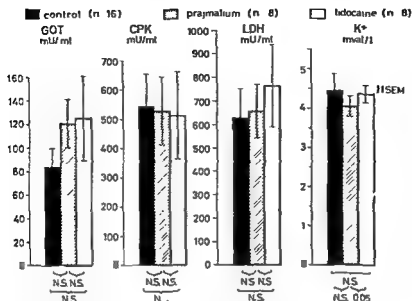
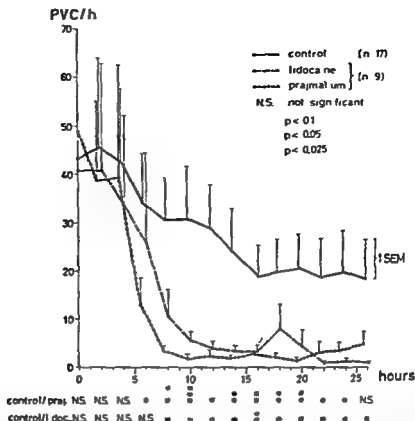


Fig 2 The mean peak enzyme values of GOT, CPK, LDH and serum potassium are shown for all three groups. Enzyme values, especially creatine kinase values, did not differ significantly, indicating comparable infarct sizes. Serum potassium values were lower in the prajmalum group than in the lidocaine group.

Table 1 Absolute values of premature ventricular complexes per hour (PVC/hr) in the control group and in both treated groups during control period and in the following hours (hr) values represent mean  $\pm$  standard error of the mean (SEM)

	Control period	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr	26 hr
control group (n = 11)	43.4 $\pm$ 13.5	45.5 $\pm$ 18.5	43.2 $\pm$ 15.7	34.2 $\pm$ 10.2	30.6 $\pm$ 8.6	30.7 $\pm$ 9.6	27.7 $\pm$ 10.8	23.6 $\pm$ 8.8	18.6 $\pm$ 6.4	20 $\pm$ 6.8	20.7 $\pm$ 7	18.6 $\pm$ 8	19.9 $\pm$ 8.5	18.8 $\pm$ 8.2
prajmalum num bi tartrate (n = 9)	49.2 $\pm$ 20.9	39 $\pm$ 16.4	39.6 $\pm$ 23.4	13 $\pm$ 5.5	3.5 $\pm$ 0.9	1.7 $\pm$ 0.8	2.3 $\pm$ 1.4	1.8 $\pm$ 0.8	2.6 $\pm$ 1.4	2 $\pm$ 0.8	1.3 $\pm$ 0.7	3.1 $\pm$ 2.3	3 $\pm$ 1.8	4.9 $\pm$ 7
lidocaine (n = 9)	40.8 $\pm$ 11.4	40.8 $\pm$ 27.3	33.6 $\pm$ 21.8	26 $\pm$ 18.7	10.6 $\pm$ 5.8	5.3 $\pm$ 2.1	4 $\pm$ 1.5	3.4 $\pm$ 1.2	3.3 $\pm$ 1.4	6.2 $\pm$ 5.1	4.5 $\pm$ 3.5	1.1 $\pm$ 0.4	1 $\pm$ 0.6	0.6 $\pm$ 0.2
control vs prajmalum 2 P	ns	ns	ns	<0.10	<0.025	<0.025	<0.10	<0.05	<0.05	<0.05	<0.05	<0.10	<0.10	ns
control vs lidocaine 2 P	ns	ns	ns	ns	<0.10	<0.05	<0.10	<0.10	<0.05	<0.10	<0.10	<0.10	<0.10	<0.10
prajmalum vs lidocaine 2 P	ns	ns	ns	ns	ns	<0.10	ns	ns	ns	ns	ns	ns	ns	ns

ns = not significant; n = number of patients



**Fig 3** Frequency of premature ventricular complexes per hour (PVC/h) during the total investigation period. There was a mild increase and subsequent slow decrease of ectopic beats in the control group. With both medications, lidocaine and prajmalum bitartrate there was a marked decrease in premature ventricular complexes. A significant difference was found in the control group after 6 hours under prajmalum bitartrate and after 8 hours under lidocaine administration. Mean  $\pm$  1 standard error of the mean (SEM).

prajmalium bitartrate the frequency of premature ventricular complexes was reduced to 13 PVC/hr as compared to 34 PVC/hr in the control group. Eight hours after onset of therapy patients treated with lidocaine had 11 PVC/hr compared to 31 PVC/hr in the control group. Ten hours after onset of therapy the frequency of premature ventricular complexes was reduced to 17 PVC/hr under prajmalium and to 53 PVC/hr under lidocaine while patients of the control group had 31 PVC/hr (Fig 3 and Table II).

In all patients the frequency of premature ventricular complexes per hour during the control period prior to medication was listed as 100% (Fig 4 and Table II). While in control patients premature ventricular complexes increased an immediate reduction was registered in the prajmalum and in the lidocaine group. A significant difference however was noted only 6 hours after the onset of therapy. After 8 to 10 hours with medication the peak drug effect was reached when

premature ventricular complexes were reduced to 6% under prajmalium and to 20% under lidocaine administration. PVCs in the control group amounted to 180%.

The frequency of premature ventricular complexes was only once (10th hour) significantly lower under prajmalium bitartrate compared to lidocaine administration. In general there was no significant difference in the drug effect of both medications.

**Runs of premature ventricular complexes**  
Runs of premature ventricular complexes increased markedly in the control group especially during the first 4 hours (26.5%). Thereafter runs decreased spontaneously to varying degrees. Under lidocaine runs also increased initially but were clearly reduced thereafter. Although runs of premature ventricular complexes occurred less frequently under lidocaine than in the control group there was no significant difference between groups (Fig. 1 and Table III).

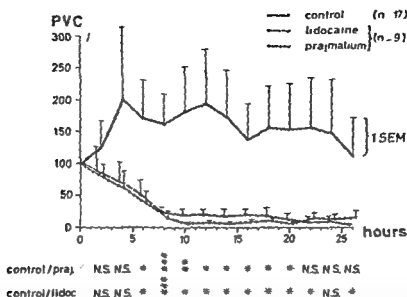


Fig. 4 Frequency of premature ventricular complexes during the control period is listed as 100 percent. In the control group premature ventricular complexes further increased, whereas in both treatment groups ectopic beats were immediately reduced. After the sixth hour a significant difference was seen in the control group. Prajmalum bitartrate's effects appear earlier and are more pronounced than the effects of lidocaine.

II Frequency of premature ventricular complexes in percent (PVC in %) of the control period in the control group and in both treated groups. values represent mean  $\pm$  standard error of the mean (SEM)

	Control period	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr	26 hr
control group (n = 17)	100	124 $\pm 41$	200 $\pm 107$	169 $\pm 47$	180 $\pm 70$	197 $\pm 86$	171 $\pm 74$	137 $\pm 16$	154 $\pm 64$	153 $\pm 72$	154 $\pm 78$	145 $\pm 84$	111 $\pm 60$	
prajmalum bitartrate (n = 9)	100	81 $\pm 18$	67 $\pm 25$	37 $\pm 19$	14 $\pm 7$	5 $\pm 2$	6 $\pm 2$	5 $\pm 2$	8 $\pm 3$	9 $\pm 4$	4 $\pm 2$	13 $\pm 9$	11 $\pm 7$	14 $\pm 10$
lidocaine (n = 9)	100	87 $\pm 32$	71 $\pm 30$	51 $\pm 23$	25 $\pm 7$	20 $\pm 9$	20 $\pm 11$	18 $\pm 9$	20 $\pm 12$	18 $\pm 13$	13 $\pm 8$	8 $\pm 6$	10 $\pm 8$	4 $\pm 2$
control vs prajmalum	n.s.	n.s.	<0.1	<0.025	<0.05	<0.1	<0.1	<0.1	<0.1	<0.1	n.s.	n.s.	n.s.	
control vs lidocaine	n.s.	n.s.	<0.1	<0.025	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	n.s.	<0.1	
prajmalum vs lidocaine	n.s.	n.s.	n.s.	n.s.	0.1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	

n.s. = not significant; n = number of patients; hr = hrs

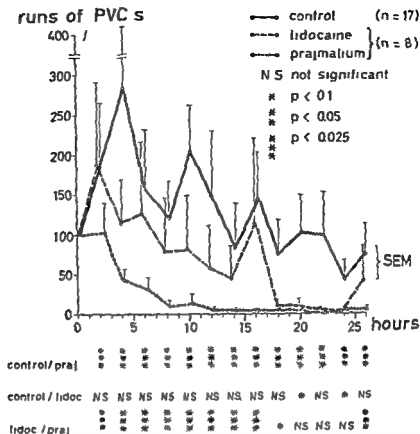


Fig 5 This figure illustrates the frequency of runs of premature ventricular complexes in percent of the control period. There was a significant increase (285 percent) in the control group within the first 4 hours, with a subsequent intermittent decrease. Under lidocaine administration there was an initial increase and thereafter a marked reduction. The difference to the control group was not significant. Under prajmalium bitartrate administration there was no initial increase. Subsequently an effective and significant reduction of runs of premature ventricular complexes was manifested.

Under prajmalium bitartrate runs of premature ventricular complexes did not increase. Runs were quickly and effectively reduced to between 4 and 1% in the twelfth hour. There was a significant difference to the control group after 2 hours with medication. It should be noted that runs of such complexes were also significantly reduced when compared to the lidocaine group (Fig 5 and Table III).

### Discussion

It is particularly difficult to study the efficacy of antiarrhythmic drugs in the acute stage of myocardial infarction. The individual frequency of premature ventricular complexes varies largely from patient to patient. Following infarction an initial increase in ectopy is followed by a moderate spontaneous decrease. Therefore a control group with no antiarrhythmic medication is needed in any such study. Furthermore, patient groups should be statistically comparable with

regard to time elapsed between infarction and onset of therapy, infarct localization, mean age, infarct size (CK values) and potassium values.

The present findings document similar drug effects of both oral prajmalium bitartrate and intravenous lidocaine in the reduction of premature ventricular complexes in acute myocardial infarction. Therapeutic doses of both drugs were given i.e. 20 mg prajmalium bitartrate orally every 4 hours and 2 l mg /minute lidocaine intravenously. Prajmalium bitartrate seems to have a more pronounced peak effect. In three of the patients who received an initial bolus injection of 100 mg of lidocaine premature ventricular complexes were not more rapidly reduced than in the remaining six patients.

In general antiarrhythmic drug effects seem to be limited during the early phase of acute myocardial infarction. In both treated groups premature ventricular complexes were reduced slowly. In the control group premature ventricular com-

III Runs of premature ventricular complexes in the control group and in both treated groups frequency of runs during control period is listed as 100 percent—time elapsed since beginning of hr = hours (values represent mean  $\pm$  standard error of the mean [SEM])

	Control period	2 hr	4 hr	8 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr	26 hr
group (n = 17)	100	192 ± 74	285 ± 128	159 ± 73	119 ± 47	204 ± 58	149 ± 72	81 ± 50	144 ± 60	75 ± 43	104 ± 46	100 ± 54	43 ± 21	70 ± 39
prajmalum bitartrate (n = 8)	100	101 ± 30	42 ± 14	30 ± 14	8 ± 8	17 ± 8	4 ± 4	3 ± 3	1 ± 1	1 ± 1	1 ± 1	0 ± 0	1 ± 1	1 ± 1
control (n = 8)	100	188 ± 100	115 ± 53	177 ± 90	79 ± 68	82 ± 68	58 ± 57	42 ± 42	113 ± 109	8 ± 8	7 ± 7	1 ± 1	0 ± 0	42 ± 47
prajmalum bitartrate vs control		<0.005	<0.0005		<0.0005		<0.0005		<0.0005		<0.0005		<0.0005	
lidocaine 2 P		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	<0.1	n.s.	<0.1	n.s.
prajmalum bitartrate vs lidocaine	2 P	<0.0005	<0.0005		<0.0005		<0.0005		<0.0005	<0.1	n.s.	n.s.	n.s.	<0.0005

n.s. = not significant n = number of patients.

complexes and runs of such complexes still increased at this stage.

Runs of premature ventricular complexes were effectively reduced under prajmalum bitartrate. There was however no significant effect on frequency of such runs in the lidocaine group. Apparently runs of premature ventricular complexes were more effectively reduced under prajmalum bitartrate than under lidocaine. However this may be due to the relatively low dose of lidocaine used.

**Prajmalum bitartrate** During the first two weeks after the onset of therapy prajmalum bitartrate reduced premature ventricular complexes by 16%. Wette and Nieh<sup>7</sup> reported on the effect of drug effect after one hour. The duration of the drug effect lasted 5 to 6 hours. The known side effects of the drug are QRS enlargement at higher doses and cholestasis during chronic application in rare cases.<sup>2</sup> In this study it should be noted that QRS complexes did not enlarge and heart failure was not aggravated.

Various long term studies confirmed the effect

of prajmalum bitartrate.<sup>2, 13, 16, 17, 19, 21, 27</sup> In these papers a considerable low rate of side effects such as gastrointestinal disorders, QRS widening and intrahepatic cholestasis have been reported.<sup>2, 13, 21, 22, 25</sup> Administration of more than 3 mg/kg body weight caused intoxication.

**Lidocaine** Lidocaine remains the standard drug in the treatment of acute myocardial infarction. Bearing in mind the spontaneous increase in the frequency of ectopic beats in the control group it cannot be assumed that compared to oral medication lidocaine reduces premature ventricular contractions abruptly to zero even if an initial bolus had been administered in every patient.

Many authors favor the administration of an initial bolus injection of lidocaine.<sup>2, 13, 16, 17</sup> We comply with this recommendation only in part and favor a bolus injection only in patients with a high rate of ventricular ectopic beats. Furthermore in the presence of intraventricular conduction disturbances or multiple arrhythmias a slow onset of therapy seems advisable as is evident



from the literature.<sup>30</sup> Side effects have frequently been reported after bolus injections.<sup>31-33</sup> According to Borer and associates,<sup>3</sup> a bolus injection with a subsequent permanent infusion does not favorably affect fibrillation threshold. Considering that it takes 6 to 8 hours before the full drug effect is reached, a bolus injection with a half life of 20 minutes cannot have a major permanent effect.<sup>34</sup>

In only three of the nine treated patients was a bolus injection of 100 mg of lidocaine necessary in this study because of frequent ventricular ectopic beats. In these three patients the reduction of premature ventricular complexes was not more rapid than in those patients not given a bolus injection. In general, however, one or two bolus injections have to be recommended to reach therapeutic blood levels of lidocaine in an appropriate time period.

In the literature recommendations for the prophylactic use of antiarrhythmic drugs in patients with acute myocardial infarction are contradictory to date. Lie and colleagues<sup>35</sup> reported a significant decrease in the frequency of ventricular fibrillation in patients with acute myocardial infarction who initially received a bolus injection of 100 mg and subsequently 3 mg/minute of lidocaine over a period of 48 hours. Mogensen and co-workers<sup>36</sup> had similar results. Bleifeld and associates<sup>37</sup> however found no difference in the frequency of premature ventricular complexes after the prophylactic administration of lidocaine as compared to an untreated control group. Ramdohr and Wirtzfeld and colleagues<sup>38</sup> concluded that in general lidocaine should not be administered to prevent rhythm disturbances. Manifest disturbances, however, should be treated adequately and effectively.

Proper dosage of lidocaine was studied by Bleifeld and associates.<sup>37</sup> Many authors recommend administration of the dose used in this study.

According to Simon,<sup>39</sup> only excessively high doses of more than 7.0 mg/kg body weight may cause major side effects. In the literature drowsiness, convulsions, parasthesias, rhythm and intraventricular conduction disturbances and atrioventricular blocks have been reported following a bolus injection and infusion of lidocaine in the dosage range between 3 and 4 mg/minute.

In conclusion, a similar beneficial effect on the

frequency of premature ventricular complexes after acute myocardial infarction was found after oral administration of prajmalium bitartrate after the intravenous administration of lidocaine as compared to an untreated control group. 1 dose used oral prajmalium bitartrate became effective as early as does intravenous lidocaine. However, a bolus injection of lidocaine was in only three of the nine treated patients. Lidocaine bitartrate also significantly reduces premature ventricular complexes. Side effects were not observed either under lidocaine or prajmalium bitartrate treatment. Therefore, in the initial phase of myocardial infarction may be effectively treated with prajmalium bitartrate.

### Summary

In 35 patients with acute myocardial infarction, premature ventricular complexes were quantified from stored continuous electrocardiographic recordings using a semiautomated arrhythmia detection system. Seventeen patients separately at random received no antiarrhythmic drug and formed the control group. In nine patients, prajmalium bitartrate was given orally at a dose of 100 mg (20 mg every 4 hours). Nine patients received permanent infusions of 2.1 mg/minute of lidocaine (corresponding to a daily dose of 3 g). In the treated groups, premature ventricular complexes decreased significantly as compared to the spontaneous frequency in the control group. Six hours after the onset of therapy, premature ventricular complexes were reduced to 37% of the initial value in the prajmalium bitartrate group and to 51% in the lidocaine group, whereas in the control group the frequency increased (169%). The peak effect was reached after ten hours when premature ventricular complexes were reduced to 6% under prajmalium bitartrate and to 20% under lidocaine administration.

Runs of premature ventricular complexes were nearly completely suppressed after administration of prajmalium bitartrate. Under lidocaine administration, runs were moderately and significantly reduced. Eight hours after the onset of therapy, runs were reduced to 8% of the initial value under prajmalium bitartrate and to 79% under lidocaine. The effect of prajmalium bitartrate on runs of premature ventricular complexes was significantly more pronounced than the effect of lidocaine.

The present study documents that

administered prajmalum bitartrate is an alternative to intravenous administration of lidocaine in the treatment of ventricular arrhythmias after acute myocardial infarction

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## The rhythm of the heart in active elderly subjects

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The development of ambulatory electrocardiographic monitoring or dynamic electrocardiography (DCG) together with facilities for high speed, semiautomatic playback and analysis has provided a useful investigative tool for the diagnosis of symptoms such as syncope presyncope and palpitations.<sup>1-3</sup> The technique has also allowed a more accurate appreciation of the patterns of cardiac rhythm in normal subjects of young and middle age groups.<sup>4</sup> Previous investigators of older populations who have employed conventional 12 lead electrocardiograms (ECG) have suggested that there is a high incidence of cardiac arrhythmias in this age group,<sup>5-8</sup> and DCG studies of adult populations have revealed an increasing incidence of arrhythmias as age advances.<sup>10-12</sup> Rhythm abnormalities are so frequent in hospitalized elderly patients that it has been said that certain arrhythmias should be regarded as a normal finding.<sup>13</sup> Other authors have pointed out that there are no adequate data on the rhythm of the normal elderly heart on which to base such a statement. This study reports the results of a DCG survey of healthy old people leading active independent lives and defines the spectrum of

cardiac rhythms and arrhythmias in group

### Patients and methods

A group general practice in Sussex provided a list of all their patients 75 years and older. Of this total of 268 patients 11 who were available fit and consenting formed the unselected study group. Their age distribution is shown in Table I. None of those studied had clinical mental disease or any medical condition requiring acute attention. Although all said that they were well, insistent direct questioning did reveal an incidence of minor palpitations and occasional syncope. Eight of the group suffered mild but typical pectoris and 33% had a history of hypertension. Seventy eight percent had no history of vascular disease and 44% had no significant history. Only 17% were taking no drugs, 61% were not taking any cardioactive

tion. This heterogeneous sample comprised the study group and on each subject a clinical and physical examination and 12 lead resting ECG were performed. An Avionics television Electrocardiograph Model 42 was used to record the electrocardiogram for a sample of 24 hours. The subject was encouraged to live as near normal a day as possible and to keep a diary of the day's events and to note any symptoms which occurred during the recording.

The resting ECG was scrutinized and interpreted by one observer who had no knowledge of the results of the 24 hour DCG. A trained technician under the supervision of a card

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ulated examples of each arrhythmia which occurred during the 24 hour recording. In addition, visual ectopic counts were made over one minute during each 30 minutes of real time and heart rates averaged over a 30 second period were made each 15 minutes throughout the recording. The Avionics scanner Model 660 was used for the analysis.

Conventional criteria of rhythm analysis were employed. Ventricular ectopic beats were classified according to the scheme outlined in Table II. The results in patients aged 75 to 79 years, 80 to 84 years and 85 years and over were analyzed separately. Subgroups of patients who smoked, were hypertensive or who had evidence of coronary disease were compared with the group as a whole. Results obtained from the DCG were contrasted with those seen on the conventional ECG. The results in subjects with syncope, dizziness or palpitations were compared with those who would admit no symptoms.

Within 18 months of the start of the study, 13 had died and the 24 hour DCG results in this group were considered separately.

#### Results

In 98 cases the dominant cardiac rhythm was sinus in origin. In this rhythm the heart rate was related to the range of 50 to 100 beats/minute. 73 subjects. The heart rate fell below 50 beats/minute in only 11 cases and in seven of these bradycardia occurred only during sleep. In 15 instances the heart rate rose above 100 beats/minute but in no case did the heart rate exceed 130 beats/minute. Thirty five tapes revealed sinus rate which did not vary by more than 10 beats/minute throughout the 24 hours. The mean heart rate was slightly slower for men (70 beats/minute) than for women (76 beats/minute). This difference was significant ( $p < 0.001$ ). Sinus arrhythmia, defined as adjacent beat to beat P-P interval variation of greater than 10% was seen in only 15 of the 98 cases.

Established atrial fibrillation was noted in eight cases. Only two of these were receiving treatment for control of heart rate and in these two patients who were taking digoxin the heart rate fell intermittently below 40 beats/minute. In one other case rapid atrial fibrillation was seen with an averaged heart rate exceeding 150 beats/minute. The remaining five cases had controlled ventricular rates throughout the day of recording

Table 1 Age distribution—106 subjects

Age (yrs)	Number
75-79	46
80-84	41
85-89	14
90-94	4
> 95	1

and none of these subjects were receiving negative inotropic drugs. There were three examples of paroxysmal atrial fibrillation: two detected by ambulatory monitoring and one by conventional 12 lead ECG. In these three examples atrial fibrillation produced a rapid ventricular response.

Other supraventricular arrhythmias (Table II) occurred in 29 subjects. Of these, atrial and junctional premature contractions comprised the majority. In only one case was paroxysmal atrial tachycardia observed. There were two examples of paroxysmal junctional tachycardia. Idiojunctional rhythms were not seen although in four instances junctional escape beats were noted. Atrial flutter was not observed.

Ventricular arrhythmias were classified according to Lown and Wolf's criteria. These criteria were modified for 24 hour ambulatory monitoring for which there are no clear grading standards presently available. An isolated incidence of ventricular ectopics was defined as less than 10/hour and frequent ventricular ectopics as greater than 100/hour. Potentially serious or major ventricular arrhythmias (Table II) were seen in 32 subjects. Paroxysmal ventricular tachycardia was present in four cases.

In addition to ventricular bradycardia in response to treated atrial fibrillation, one case of intermittent complete heart block was discovered on the DCG. Otherwise there were no serious bradycardias. Sinus node arrest and exit block were not observed. However, a normal ambulatory recording which demonstrated sinus rhythm throughout, uninterrupted by ectopic beats, tachycardia or ventricular pauses was only obtained from 24 patients.

The effects of age, historical and electrocardiographic evidence of ischemic heart disease, systemic systolic hypertension and smoking habits were examined separately (Table III). No significant differences in the incidence of normality

Table II The spectrum of cardiac rhythms detected by 24 hour DCG monitoring in 106 subjects

Sinus rhythm	96
Sinus bradycardia	11
Sinus tachycardia	13
Sinus arrhythmia	15
Atrial fibrillation	11
Established atrial fibrillation	8
Paroxysmal atrial fibrillation	3
Rapid atrial fibrillation	1
Slow atrial fibrillation	1
Supraventricular arrhythmias	26
Atrial premature beats	22
Junctional premature beats	4
Atrial tachycardia	1
Junctional tachycardia	1
Junctional escape beats	4
Atrial flutter	1
Ventricular arrhythmias	10
Minor	41
Isolated ventricular premature beats (< 10/hr)	11
Moderate ventricular premature beats (10-100/hr)	11
Major	11
Frequent ventricular premature beats (> 100/hr)	11
Multiform ventricular premature beats	1
Paired ventricular premature beats	1
Ventricular bigeminy	4
Salvos of ventricular premature beats	1
Ventricular tachycardia	1

supraventricular arrhythmias or major and minor ventricular arrhythmias was found. Follow up 18 months after the ambulatory recording revealed that 13 of the 106 subjects had died. An analysis of the arrhythmia spectrum of these cases revealed no differences compared with the group as a whole. Of the 13 deaths two were sudden and unexplained and both of these subjects had major ventricular arrhythmias in one case ventricular tachycardia at the time of recording.

The single 12 lead electrocardiogram taken on the day of ambulatory recording demonstrated entirely normal sinus rhythm in 72 instances. Ten recordings demonstrated atrial fibrillation and there were 16 traces demonstrating other supraventricular arrhythmias and 16 examples of major ventricular arrhythmias. Comparison with the results of ambulatory monitoring (Table IV) reveal that arrhythmias were detected two to four times more frequently by ambulatory recording than by the conventional 12 lead ECG.

Although each patient was encouraged to complete a diary of daily events and of any symptom suffered during the recording compliance was very poor and direct comparison between symp-

toms and DCG findings was impossible. The occurrence of minor and major arrhythmias was compared with the symptoms to which each subject had admitted in the questionnaire. V) There was no correlation between the occurrence of these symptoms and the DCG. Similar ambulatory recordings were obtained from those who did and those who did not have symptoms.

### Discussion

It is debatable whether the sample employed in this study could be regarded as an entire elderly population. The frequent occurrence of syncope, palpitations, dizziness, and hypertension and the high intake of medication would suggest that the group is not representative of criteria which would apply to younger subjects. However, insistence on strict normality would exclude all but 12 members of the 268 patients. The elderly patients cared for by a geriatric practice. Instead, all the elderly patients in this practice who were mentally competent and free from acute medical complaints and who were willing to take part in the study were included. This group probably represents the

Table III The distribution of normal and abnormal recordings detected by 24 hour DCG monitoring the whole group and subgroups divided according to age the presence of ischemic heart disease hypertension smoking habits and deaths 18 months following the ambulatory recording

			Normal	Supraventricular arrhythmias	Minor ventricular arrhythmias	Major ventricular arrhythmias
Total			24 (23%)	29 (27%)	41 (39%)	32 (30%)
Age	75-79	46	10 (22%)	10 (22%)	17 (37%)	16 (35%)
	80-84	41	10 (24%)	15 (36%)	16 (39%)	9 (22%)
	> 85	19	4 (21%)	4 (21%)	8 (42%)	7 (37%)
Ischemic heart disease	Present	31	6 (25%)	7 (29%)	8 (33%)	7 (29%)
	Absent	82	18 (22%)	22 (27%)	33 (40%)	25 (28%)
Systolic blood pressure	< 160	72	16 (22%)	18 (25%)	29 (40%)	21 (29%)
	160-220	31	8 (26%)	10 (32%)	10 (32%)	10 (32%)
	> 220	3	0	0	2 (66%)	1 (33%)
Tobacco	Non smoker	87	20 (24%)	21 (26%)	33 (40%)	23 (28%)
	Smoker	24	4 (17%)	8 (33%)	8 (33%)	9 (38%)
Deaths	All	13	1 (8%)	6 (46%)	5 (38%)	5 (38%)
	Sudden	2	0	1 (50%)	1 (100%)	2 (100%)

ambulant population at large more closely than an artificially selected group of strictly normal subjects

Old people are generally reluctant to cooperate in studies of this kind which intrude on their privacy. Sixty eight of the 217 people canvassed on our invitation to take part in the study of those who did participate some found the recording equipment cumbersome and others were frightened by the procedure. Despite our encouragement to the contrary these various factors probably modified the participants' activity during the day or recording and may have affected the validity of our results. These difficulties could not be avoided but were minimized by using the recorders and taping the DCG in the subjects' own homes. Another technical difficulty encountered during this study was the inability of this group to accurately complete the diary of symptoms noted during the day of recording. This item is not confined to the older patient<sup>10</sup> but did prevent any direct comparison between symptoms suffered and DCG findings.

It is generally accepted that sinus rates decrease linearly with age but in our study sinus bradycardia was uncommon. In comparison the incidence of severe sinus bradycardia in a series of 50 students was 24%. Our findings are consistent with previous studies using the 12 lead ECG or rhythm strips. In his review of the surface ECG

Table IV Comparison of arrhythmias detected by 12 lead ECG and 24 hour DCG

	24 hr DCG	12 lead ECG
Normal	21 (23%)	72 (68%)
Atrial fibrillation	10 (9%)	9 (9%)
Supraventricular arrhythmias	29 (27%)	10 (15%)
Minor ventricular arrhythmias	41 (39%)	9 (19%)
Major ventricular arrhythmias	32 (30%)	16 (15%)
Complete heart block	1 (1%)	0

of patients over 70 years of age Gavey<sup>1</sup> reported only a 2.5% incidence of sinus bradycardia and Kirk and Kvorning<sup>2</sup> noted a lower incidence of sinus bradycardia in patients over 65 years (5.8%) compared with patients below the age of 40 years (9.3%). These authors also contended that sinus bradycardia is seen more frequently in patients with acute medical problems and the relatively low incidence of slow sinus rates in this study may be related to the generally healthy and ambulant nature of the study population.

Although sinus arrhythmia was not frequently encountered in this study its incidence is consistently higher than in previous ECG studies.<sup>11</sup> More surprising was the severe restriction in the dynamic range of heart rates in one third of this

Table II The spectrum of cardiac rhythms detected by 24 hour DCG monitoring in 106 subjects

Sinus rhythm	94 (88%)
Sinus bradycardia	11 (10%)
Sinus tachycardia	15 (14%)
Sinus arrhythmia	15 (14%)
Atrial fibrillation	11 (10%)
Established atrial fibrillation	8 (8%)
Paroxysmal atrial fibrillation	3 (3%)
Rapid atrial fibrillation	1 (1%)
Slow atrial fibrillation	2 (2%)
Supraventricular arrhythmias	29 (27%)
Atrial premature beats	22 (21%)
Junctional premature beats	3 (3%)
Atrial tachycardia	1 (1%)
Junctional tachycardia	2 (2%)
Junctional escape beats	4 (4%)
Atrial flutter	0
Ventricular arrhythmias	73 (68%)
Minor	
Isolated ventricular premature beats (< 10/hr)	46 (43%)
Moderate ventricular premature beats (10-100/hr)	15 (14%)
Major	
Frequent ventricular premature beats (> 100/hr)	13 (12%)
Multiform ventricular premature beats	3 (3%)
Paired ventricular premature beats	4 (4%)
Ventricular bigeminy	5 (5%)
Salvos of ventricular premature beats	2 (2%)
Ventricular tachycardia	4 (4%)

supraventricular arrhythmias or major and minor ventricular arrhythmias was found. Follow up 18 months after the ambulatory recording revealed that 13 of the 106 subjects had died. An analysis of the rhythm spectrum of these cases revealed no differences compared with the group as a whole. Of the 13 deaths, two were sudden and unexplained and both of these subjects had major ventricular arrhythmias in one case, ventricular tachycardia at the time of recording.

The single 12 lead electrocardiogram taken on the day of ambulatory recording demonstrated entirely normal sinus rhythm in 72 instances. Ten recordings demonstrated atrial fibrillation and there were 16 traces demonstrating other supraventricular arrhythmias and 16 examples of major ventricular arrhythmias. Comparison with the results of ambulatory monitoring (Table IV) reveal that arrhythmias were detected two to four times more frequently by ambulatory recording than by the conventional 12 lead ECG.

Although each patient was encouraged to complete a diary of daily events and of any symptom suffered during the recording, compliance was very poor and direct comparison between symp-

toms and DCG findings was impossible. However, the occurrence of minor and major arrhythmias was compared with the symptoms to which subject had admitted in the questionnaire (Table V). There was no correlation between the occurrence of these symptoms and the DCG findings. Similar ambulatory recordings were found in those who did and those who did not have symptoms.

### Discussion

It is debatable whether the sample employed in this study could be regarded as an entirely representative elderly population. The frequent occurrence of syncope, palpitations, dizziness, chest pain, hypertension and the high intake of medication would suggest that the group is not normal, criteria which would apply to younger age groups. However, insistence on strict normality would exclude all but 12 members of the 268 patients, years or older, cared for by a group general practice. Instead, all the elderly patients in this practice who were mentally competent, free from acute medical complaints and who consented to take part in the study were included. This group probably represents the elderly

symptomatic patients. The study was performed on 106 subjects at home and consisted of a clinical questionnaire, physical examination, resting 12 lead ECG and 24 hour taped DCG.

Eight subjects had established atrial fibrillation (AF) and three had paroxysmal AF. Established AF resulted in a rapid ventricular response in one case and a slow ventricular rate in two. A controlled ventricular response was found in five subjects who were on no treatment.

Of 98 subjects in sinus rhythm, 73 had a heart rate of between 50 and 100 beats/minute, 11 had sinus bradycardia, and in only 15 instances did the heart rate intermittently exceed 100 beats/minute. Thirty-five subjects had sinus rates that did not vary by more than 10 beats/minute throughout the 24 hours.

The DCG demonstrated isolated ventricular premature beats in 45 subjects and potentially more serious ventricular arrhythmias in 32 cases. Ventricular bradycardias of any variety were rarely seen. Arrhythmias were detected two to four times more frequently by DCG than by 12 lead ECG. Within this sample age, ischemic heart disease, systolic hypertension, smoking habits, and a history of syncope, palpitations, or dizziness did not affect the prevalence of any type of arrhythmia.

The results of this study demonstrate that although ectopic cardiac rhythms and tachycardias are common in apparently healthy elderly people, ventricular pauses and bradycardias are extremely uncommon.

Our thanks are due to Dr. Ivan Clout, his partners and staff, both for their help and for allowing us to investigate patients in their practice.

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## Serum chromium in patients with recent and old myocardial infarction

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Persons dying of coronary heart disease were found to have virtually no chromium in their aortas whereas those dying of accidents or other diseases had aortic chromium. Chromium levels in tissues of Americans tended to be low and declined with age, whereas tissues of Africans and Orientals contained much higher concentrations. Tissues of Thais had more chromium than any other group and they also had a very low incidence of aortic atherosclerosis.

Chromium deficiency has also been linked with an impairment of glucose tolerance, elevated serum cholesterol levels, and the causation of aortic plaques in animals.

These findings have led to the conclusion that decreased or absent aortic chromium in atherosclerosis reflects the decreased or absent chromium in the coronary arteries and that this condition leads to abnormal metabolism and plaque formation.

The measurement of plasma chromium has until recently presented technical difficulties and no information is available regarding the blood levels of chromium in patients suffering from acute myocardial infarction or known to have coronary artery disease.

### Patients and methods

Forty-five patients without serious diseases were seen in the outpatient clinic and 10 volunteers were taken as controls. Diabetics (fasting blood glucose of over 110 mg/dl) were excluded and no patient had a clinical or electrocardiographic evidence of ischemic or rheumatic heart disease, arteriosclerosis, tension or congestive cardiac failure. No patient was receiving medication.

Thirty-four patients attending the outpatient clinic who had been hospitalized 6 to 12 months previously with proven myocardial infarction were taken as the test group. Any patient with a fasting blood glucose level of over 110 mg/dl was also excluded from the study.

Thirty-seven patients consecutively admitted with a definite diagnosis of myocardial infarction (that is typical history and electrocardiographic changes together with elevation of serum aspartate aminotransferase and LDH) were also studied and the chromium was determined the morning after admission, 1 to 4 days later and again 5 to 7 days following admission.

Finally, the serum chromium was measured in 14 patients who were either diabetic or who were receiving intravenous glucose. The latter patients with chest pain who did not have electrocardiographic or enzyme changes.

Serum chromium was measured by absorption spectrophotometry as described by Pekarek and associates. In each case, samples were taken in polyethylene test

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er an overnight fast and were kept at  $-20^{\circ}\text{C}$  for analysis

There were 32 males and 13 females in the control group and their ages ranged from 22 to 90 years (mean 49.9 years). The mean serum chromium was 1.71 parts per billion (ppb) (SE 0.14).

Thirty-four patients (25 males and nine females) aged 42 to 85 years (mean 59.1 years) with ischemic heart disease (IHD) all of whom had previously proven myocardial infarct 6 to 12 months previously had a mean serum chromium level of 1.84 ppb (SE  $\pm 0.18$ ).

Analysis of both groups showed no significant differences due to sex or age nor was there any significant difference between the mean serum chromium levels of the two groups.

*Serum chromium levels in 37 patients during the first 24 hours following a myocardial infarct* were not significantly different from our control population. However there was a significant rise during the next four days to a maximum level of 6.36 ppb (SE  $\pm 0.51$ ,  $p < 0.001$ ), followed by a subsequent fall to normal levels during the 5 days.

The serum chromium in five of these patients between 2.9 and 3.3 ppb that is just below mean plus 2 standard deviations (3.5 ppb) of the control group.

The serum chromium levels in 22 patients who were not in cardiac failure was positively correlated with infarct size as assessed by the maximum rise in SGOT ( $r = 0.5036$ ,  $p < 0.05$ ). There was no evidence of any relationship between serum chromium levels and the presence or absence of cardiac failure.

There was no increase in serum chromium levels in the 14 patients with raised blood glucose levels (diabetic subjects or patients receiving glucose infusions) nor was there any correlation between blood glucose levels and serum chromium in the patients with acute myocardial infarction.

## Discussion

The level of serum chromium found in our normal control group compares with recently published data in which a mean of 1.58 ppb (SE  $\pm 0.08$ ) was found in healthy volunteers.

We found no statistical difference in the mean serum chromium levels between patients known to have IHD and those without any clinical evidence of the disease. Thus by no means does this exclude the possibility that the patients in the control group had pathological coronary (or for that matter any other) arteries; however they were symptom free and had no obvious evidence of atherosclerotic disease. All our patients came from Jerusalem and drank the same water and so presumably had the same intake of chromium. However solitary plasma chromium levels are said not to provide a valid index of chromium nutritional status. Nevertheless we have been unable to find evidence of an association between the serum chromium level and the presence or absence of clinically evident ischemic heart disease.

Soon after an acute myocardial infarction there is a significant though temporary increase in serum chromium levels. This may be due to release from the damaged myocardial tissue as is suggested by the significant correlation with the maximum rise in SGOT. However whether the lower concentrations of chromium found in the tissues of patients who have died from their infarct is an acute phenomenon or an accompaniment of their atherosclerotic heart disease is not yet clear.

Since all our patients were receiving glucose infusions during the acute stage of their myocardial infarction and since the infarction itself may lead to a temporary impairment of glucose tolerance the serum chromium levels may have been influenced by changes in the blood glucose. Others have indeed reported that an oral glucose challenge results in a temporary increase in plasma chromium levels. However we found no correlation between serum chromium and blood glucose levels in the 14 patients we examined (with raised blood glucose levels) nor was there any correlation between serum chromium and blood glucose levels in the patients with acute myocardial infarction.

## Summary

The serum chromium in 45 subjects with no clinical evidence of ischemic heart disease was found to be 1.71 parts per billion (ppb) (SE  $\pm 0.14$ ). In 34 patients with a previously documented myocardial infarction it was 1.84

ppb ( $SE \pm 0.18$ ) The difference was not significant nor was there any difference with age or sex In 37 patients with acute myocardial infarction the serum chromium level rose to a mean of  $11.36$  ppb ( $SE \pm 0.51$   $p < 0.001$ ) during the first five days following the infarct returning to normal over the next five days There was no correlation between the serum chromium and blood glucose levels in these patients or in a further 14 patients who were receiving glucose infusions (chest pain without electrocardiographic or enzyme changes) or who were diabetics

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## Angina after bypass surgery by early and late arteriography

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Aortocoronary bypass surgery has been accepted as an effective therapy in the management of selected symptomatic patients with documented coronary artery disease. Although bypass surgery has been followed in some studies by improvement in left ventricular function,<sup>1</sup> the role of this surgical treatment in prolonging life remains controversial at present.<sup>2-4</sup> Symptomatic patients and a better quality of life<sup>5</sup> can be anticipated in the majority of patients undergoing successful bypass surgery. Recurrent angina, however, in the late follow-up period is not unusual.<sup>6-8</sup> The anatomical basis of recurrent angina pectoris after apparently successful bypass surgery requires clarification. In the present report describes the clinical and anatomical correlates of early and late postoperative angiography in 98 patients evaluated after successful aortocoronary bypass surgery.

### Material and methods

Between December 1970 and April 1977 a total of 937 patients underwent isolated aortocoronary bypass surgery. There were 14 (1.4%) operative deaths. Just prior to discharge and after informed consent, 570 patients had repeat arteri-

ography to evaluate the patency and morphologic aspects of their coronary bypass surgery. This report describes our experience in 98 of these patients who in their initial postoperative study demonstrated patency of all surgically implanted grafts. This initial postoperative study (< 2 weeks) is a routine procedure offered and performed as part of the overall evaluation of patients prior to discharge from the hospital. Each of these 98 patients had a second late follow-up arteriographic study (five to 73 months average 2.6 years) after surgery. The second angiogram was done either for recurrence of angina pectoris or in patients without symptoms to evaluate the late results of aortocoronary bypass surgery. In this asymptomatic group no criteria were used in selection except the willingness of the patient to participate. Surgical methods and diagnostic techniques used in these patients have been previously described.<sup>14</sup> The study group included 79 men and 19 women with an age range of 33 to 69 years (average 53 years). The clinical information on each patient included data regarding hypertension, diabetes mellitus, cigarette smoking, family history, and blood lipids. Cholesterol and triglyceride levels were obtained at the initial study and were considered abnormal when above the 95th percentile for age and sex as defined by Goldstein and co-workers<sup>15</sup> for a control population.

A total of 177 grafts (1.8 grafts/patient) including six internal mammary artery grafts, were implanted. Thirty-four patients had single grafts, 51 had double grafts, 11 had triple grafts and two had quadruple grafts. In order to facili-

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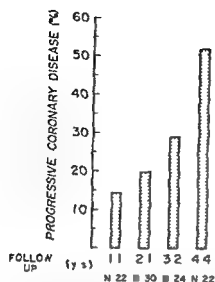


Fig 1 Frequency of progressive coronary artery disease (percent of patients) as related to the period of follow up. The latter period is the time interval between the initial and late postoperative arteriographic study.  $N$  = number of patients at each interval.

tate the postoperative graft visualization study, a metal clip was sutured to the aortic wall at the origin of each saphenous vein bypass. Closure was considered present when both selective and aortic root injection failed to visualize the bypass graft. In the majority of instances graft closure was accompanied by a dimple in the aortic wall adjacent to the metal clip. Incomplete surgical revascularization was considered present if all major coronary arteries with significant occlusive disease could not be grafted. In many such instances the diseased vessel was either completely blocked without any visible run off demonstrated diffuse disease could not be identified at the time of surgery or was considered too small for grafting. Progressive coronary disease was considered present if a new area of significant disease was found in the late postoperative study which was either previously normal or only slightly irregular. Significant new disease was defined as over 50% narrowing of a coronary artery segment. Progressive coronary disease was evaluated in both nongrafted arteries and in grafted arteries distal to the anastomoses. Segments of the coronaries proximal to grafts were not fully evaluated since in the late arteriographic studies the state of these segments could not always be determined. Standard statistical methods were used to calculate Student's  $t$  test for unpaired data and Chi-square analysis for significance.

Table 1 Angiographic correlates on late postoperative evaluation

Recurrent angina pectoris	Present	Absent	
Number of patients	38	60	
	%	n	Significance
Progressive coronary disease	47	14	$p < 0.01$
Incomplete surgical revascularization	37	15	$p < 0.05$
Graft closure	21	5	$p < 0.05$
Graft stenosis	11	5	$p < 0.05$
Any one of above factors	97	36	$p < 0.01$

## Results

Of the 98 patients evaluated 38 were referred for recurrent angina pectoris. Comparison of these 38 symptomatic patients with the remaining 60 without angina revealed no significant differences in age or incidence of hypertension, diabetes mellitus, cigarette smoking, prior myocardial infarction, or abnormal serum lipid levels. There was no significant difference in the time interval between early and late postoperative studies in symptomatic or symptom-free subjects. Recurrence of symptoms occurred between 6 and 59 months after surgery (average 24 mos).

**Progressive coronary artery disease** (Table 1) was present in 47% of patients with recurrent angina compared to 18% in asymptomatic patients ( $p < 0.005$ ). No particular coronary artery demonstrated any predilection to develop progressive disease. In the entire group of 98 patients, significant progression of coronary disease in the late arteriographic study of these 16 (55%) had recurrent angina. A completely new, significant coronary artery lesion in the late postoperative arteriographic study was found in 29 (24%) of 121 ungrafted major coronary arteries while in 164 patent grafts the run-off of the native coronary vessel distal to the anastomosis revealed the development of significant relesions in five instances (3%). In 13 vessels occluded by completely occluded grafts, significant progressive disease was observed in five and incomplete occlusion of the original stenotic segment in two vessels. A comparison of the clinical profile in the 29 patients with progressive coronary disease and the remaining 69 patients without new significant lesions is shown in Table II. The ages of the patients as well as the medical

Table II Clinical profile in patients with and without progressive coronary artery disease

Number (mean $\pm$ 1 SD)	No progressive disease 69	Progressive coronary disease present		Significance
		29		
	54 $\pm$ 8	51 $\pm$ 7		
	%	%		
Hypertension	40	40		N.S.
Diabetes mellitus	12	14		N.S.
Cigarette smoking	57	64		N.S.
Family history of				
Coronary artery disease	57	68		N.S.
Hypertension	46	27		N.S.
Diabetes mellitus	26	32		N.S.
Cholesterol				
Mean $\pm$ 1 SD (mgm/dl)	239 $\pm$ 37	264 $\pm$ 57		p < 0.05
Percent abnormal	8	11		N.S.
Triglyceride				
Mean $\pm$ 1 SD (mgm/dl)	168 $\pm$ 79	174 $\pm$ 86		N.S.
Percent abnormal	23	27		N.S.

hypertension diabetes mellitus cigarette smoking or elevated serum lipids showed no significant difference the mean serum cholesterol (mg/dl) was 264  $\pm$  57 in the group with progressive disease compared to 239  $\pm$  37 in those without progressive disease ( $p < 0.05$ ). Postoperative cessation of smoking or decreased lipid levels at late postoperative study did influence the results shown in Table II. The incidence of progressive coronary artery disease directly related ( $p < 0.025$ ) to the time interval between the early and late postoperative study (Fig 1). The average incidence of progressive disease was 10.7% of patients per year.

Incomplete surgical revascularization (Table I) was noted in 37% and 15% of patients respectively with and without recurrent angina pectoris.

Of these 23 patients with incomplete surgical revascularization 14 (61%) were operated during the first 18 months of our experience with coronary bypass surgery. The remaining nine patients underwent surgery during the following five years.

Graft closure was present in 21% and 5% respectively of patients with and without angina ( $p < 0.025$ ). All six internal mammary artery grafts to the left anterior descending artery were patent while 13 (76%) of 171 saphenous vein grafts demonstrated late closure. This represents an average annual attrition rate (average percent saphenous grafts closed/yr) of 3%. Nine patients

had one graft closed two had two grafts closed and the remaining 87 patients (89%) showed patency of all grafts. However in the latter group five patients (two with angina) demonstrated over 50% localized segmental narrowing (graft stenosis) of the saphenous vein bypass (Table I). Thus 84% of patients studied angiographically after an average follow up of 2.6 years demonstrated all grafts patent and technically satisfactory—i.e. no kinks localized stenosis or stenosis at anastomotic site. Similarly no angiographic evidence of new significant lesions could be found in 70% of patients during the same follow up period.

In 92% of patients with angina pectoris at least one factor (see Table I) was present which could logically explain the presence of recurrent angina compared to 36% in asymptomatic restudied patients ( $p < 0.005$ ). Twenty six patients had only one factor predisposing to recurrent angina. These included 14 with progressive coronary disease seven were incomplete surgical revascularization four with graft closure and one with graft stenosis.

## Discussion

The beneficial effect of coronary bypass surgery in the relief of angina pectoris is firmly established. Sheldon and associates<sup>7</sup> reported 87% of patients free of symptoms after successful surgical revascularization. Schroeder and col-

leagues<sup>12</sup> noted that 97.5% of patients undergoing bypass surgery for unstable angina were either free of symptoms or had symptomatic improvement 18 months after surgery; however, at 40 months such improvement was maintained in only 83.8% of patients. It was speculated that the failure to sustain clinical improvement was due to progression of atherosclerotic disease in the native coronary circulation or to late graft occlusion or both. Others<sup>13-15</sup> have also observed late recurrence of symptoms after bypass surgery. In the present study 98 patients had initially successful bypass surgery defined as angiographically demonstrated patency of all grafts just prior to hospital discharge. During the early follow-up period (< 3 months after surgery) all patients were reported free of angina pectoris. Follow-up studies revealed that the most frequent factor associated with recurrent angina pectoris was progressive coronary artery disease in the native circulation. Such progressive disease as we have experienced may necessitate late reoperation.<sup>16-17</sup> In 14 of the 38 patients with recurrent angina progressive coronary disease with the development of a complete new significant lesion was the only factor apparently responsible for recurrent symptoms. In a study by Seides and co-workers<sup>18</sup> 16 patients asymptomatic after bypass surgery were followed for five years. In 11 late recurrent symptoms were observed. In nine of these progressive disease of the native coronary circulation was found. Seides and associates concluded that late symptomatic deterioration after bypass surgery is due for the most part to progressive disease in ungrafted vessels rather than to graft failure. The present study in a larger group of patients confirms that conclusion.

The frequency of progressive disease in ungrafted vessels was 24% and the average annual rate of progressive coronary disease was 10.7% of patients per year. In other studies<sup>19-21</sup> the rate of progressive coronary artery disease has varied from 6% to 12% of patients per year. Thus it might be anticipated that after five years half the patients undergoing bypass surgery will develop new significant lesions in ungrafted vessels. However, such speculation is unwarranted since the patients studied were a select group. The majority (64%) demonstrating such progressive disease were evaluated for recurrent angina pectoris. Thus the rate of progressive disease was 19.6% per year for patients with

recurrent symptoms compared to only 6.7% asymptomatic patients per year.

Our findings and other observations<sup>1-4</sup> indicate that coronary bypass grafts do not predispose to progressive occlusion of segments of coronary arteries distal to the anastomosis. Lawrie and associates<sup>1</sup> observed only a 1% incidence of new distal lesions in grafted vessels five years after surgery. McLaughlin and associates<sup>2</sup> have reported similar experience. The uncommon occurrence of new significant lesions distal to graft sites and the more frequent occurrence of progressive disease in nongrafted vessels (3% vs 24%) can be best explained by the predilection of atherosclerotic disease to localize at certain sites in the coronary arterial tree.<sup>22</sup> Thus aortocoronary bypass grafts are placed distal to these most vulnerable sites where significant lesions are already present. In contrast ungrafted arteries are vulnerable at these proximal sites to atherosclerotic disease. Progressive disease proximal to graft anastomoses is a common especially in the presence of high degree (> 90%) stenosis.<sup>14-15</sup> Such proximal disease appears to occur early after surgery with subsequent progression after one year. Thus a five-year follow-up reveals little or no difference in the severity of the disease in proximal segments of grafted vessels compared with nongrafted arteries.

Factors which may influence the frequency of progressive disease have been studied. The frequency of progressive coronary artery disease is directly related to the time interval between the early and late study (Fig. 1) indicating that changes are time dependent. This is consistent with observations reported by Bourassa and co-workers.<sup>21</sup> Thus at one year in nongrafted arteries serial arteriographic studies revealed a 7.3% frequency of progression compared to 41% at five years. As in the present study, hypertension, diabetes mellitus, cigarette smoking, and family history was not observed<sup>19-21</sup> to influence the frequency of progressive coronary disease. Such studies indicate that the progression of coronary disease may be influenced by serum lipid elevation<sup>22-23</sup> while others do not.<sup>24-25</sup> In the study of Bemis and associates<sup>2</sup> plasma lipid elevation was significantly associated with both the frequency and severity of arteriographic progression compared to normolipemic individuals. In a series of patients reported by Ben Zion and co-

eagues.<sup>30</sup> 44% of patients with progressive coronary disease had an elevated cholesterol compared to only 14% lacking arteriographic evidence of progression. In the present study the mean serum cholesterol for the group with progressive disease was ( $p < 0.05$ ) higher (Table II). In a pathological study by Lie and associates<sup>31</sup> hyperlipemia was associated with an increased frequency of atherosclerotic changes in the saphenous grafts. Thus after one year 78.6% of grafts from hyperlipemic individuals revealed atherosclerotic changes compared to only 11.5% from normolipemic individuals.

Incomplete surgical revascularization in most instances was the consequence of a completely blocked disease vessel without any evident run off. Diffuse distal disease, small vessel size or a distal vessel not identifiable at surgery were also common findings in patients with recurrent symptoms (Table I). It has been well documented<sup>17, 32</sup> that symptomatic improvement accompanying bypass surgery is dependent upon the completeness of revascularization. The initial improvement in our patients is not readily understood; however, only seven patients with recurrence of angina had incomplete revascularization as the only factor noted at late arteriographic study. Finally, the majority (61%) of instances of incomplete surgical revascularization were from our early surgical experience reflecting a more conservative initial approach.

Several studies<sup>33, 37</sup> indicate that most graft occlusions occur early, whereas late graft occlusion is uncommon. Late graft closure has been attributed in most instances to progression of the atherosclerotic process in the grafted artery,<sup>11</sup> whereas early graft closure has been related to fibrous intimal hyperplasia,<sup>38</sup> which does not appear to progress after the first year. In our experience with 570 patients and 1,197 grafts, early study (< 2 weeks postoperatively) revealed closure in 10.4% of grafts, whereas in a follow up period ranging from five to 73 months (average 2.6 yrs), a further 7.7% of grafts closed. In grafts found patent just prior to discharge from the hospital, the average annual rate of subsequent closure (attention rate) as reported by others<sup>39</sup> has varied from 1.7% to 3.5% of grafts per year. In the present study this average annual attention rate was 3% per year with 5.6% annually in those presenting with recurrent angina compared to only 1.1% in those without recurrent

pain. In only four instances (10.5%) was late graft closure the only factor related to recurrence of angina. In only one case was late graft stenosis found as an isolated finding. In 5% of our cases (or 3% of grafts) late graft stenosis was observed comparable to the incidence reported by others<sup>33, 34</sup> and probably related to surgical technique.<sup>9</sup>

The present study indicates that progressive coronary artery disease is the major factor related to recurrent angina pectoris after coronary bypass surgery. Late graft closure, which is not common, may also be associated with recurrent symptoms and may be related to progressive disease in distal recipient vessels. Some evidence indicates that lipid abnormalities may favor the progression of the atherosclerotic process. It is thus evident that risk factors, especially lipid abnormalities, warrant continued attention after successful surgical revascularization. Incomplete surgical revascularization will always remain a factor favoring recurrent symptoms as a result of surgical limitations imposed by the vascular anatomy. Early graft closure will continue to depend on such factors as size of vessels and run off variables which cannot be controlled. However, the major factor limiting sustained symptomatic relief after bypass surgery appears to be progression of the underlying atherosclerotic process.

### Summary

Arteriographic correlates of recurrent angina pectoris were obtained in 98 patients undergoing both early (< 2 weeks) and late (five to 70 months, average 2.6 yrs) postoperative angiography after coronary bypass surgery. All patients were discharged with arteriographic evidence of patency of all grafts (171 saphenous vein and six internal mammary artery) and all were asymptomatic during their early (< 3 month) postoperative follow up. During late follow up, recurrent angina occurred in 38 patients. The group with recurrent angina had significantly higher frequencies of progressive coronary disease (47% vs 18%), incomplete surgical revascularization (35% vs 15%), and graft closure (21% vs 5%) compared to the asymptomatic group. In the total study group, 29 (30%) had progressive coronary disease with 16 (55%) having recurrent symptoms. Progressive coronary disease was present in 24% of ungrafted vessels compared to only 3% in native coronary arteries distal to graft anastomoses. The frequency of progressive coronary disease was



directly related ( $p < 0.025$ ) to the time interval between early and late arteriographic studies. The average annual rate of progressive disease was 10.7% of patients per year. Patients with progressive coronary disease had a higher ( $p < 0.05$ ) cholesterol ( $264 \pm 57$  vs  $239 \pm 37$  mgm/dl). Incomplete surgical revascularization was more common (61%) in patients operated on during the early ( $< 15$  yrs) experience with bypass surgery. Late graft closure occurred in 7.6% of all grafts and in 11% of patients. The average annual rate (attention rate) of graft closure was 3% per year. Late graft stenosis occurred in 5% of patients but was related to angina pectoris in only one patient.

The present study indicates that late recurrent symptoms may be anticipated after bypass surgery since for the most part they are due to progressive atherosclerotic process in the native circulation. Primary graft failure plays only a minor role in producing recurrent symptoms. Thus continued control of risk factors especially lipid abnormalities is warranted after bypass surgery.

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## The effect of allopurinol on the degree of early myocardial ischemia

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The ultimate size of a myocardial infarction depends on the degree and duration of reduced blood flow to cells within the affected myocardium during an acute ischemic episode. Following obstruction of blood flow in a major coronary artery the resulting hypoxic condition downstream from the obstruction rapidly leads in sequence to reversible myocardial injury, irreversible injury, and ultimate necrosis.<sup>1-3</sup> The onset of irreversible myocardial damage probably occurs after 20 to 40 minutes of hypoxia and appears to proceed outward from the center of the involved area. Recent interest in minimizing ultimate infarct size has centered around methods of salvaging the reversibly injured ischemic cells surrounding the central zone.

Within the last decade several drug interventions such as glucose, insulin, potassium infusion, corticosteroids, nitroglycerin, propranolol, etc. have been studied for their effectiveness in protecting the ischemic myocardium.<sup>4-6</sup> Another drug that has been studied is the xanthine oxidase inhibitor allopurinol. Because of its inhibitory effect on xanthine oxidase, allopurinol effectively blocks the production of serum uric acid. For this

reason it has long been used for the treatment of gout. From earlier experiments of Crowell and associates<sup>7</sup> it was proposed that these enzyme-inhibitory properties of allopurinol may protect cell viability during hypoxia and thus protect myocardium following coronary artery occlusion. We have reported evidence in animal experiments for protection of the ischemic myocardium as well as the ischemic kidney by pretreatment with allopurinol. Treatment after occlusion was ineffective as was also reported by others.<sup>8</sup>

It was shown that early in the ischemic episode the reduced oxygen supply rapidly increases dephosphorylation of high energy phosphates within the ischemic area.<sup>9</sup> This process continues with the further breakdown of functional nucleotides terminating in the irreversible conversion of xanthine to uric acid by xanthine oxidase.<sup>10</sup> Irreversible degeneration of adenine nucleotides due to impaired oxidative phosphorylation occurs only after 25 to 30 minutes of ischemia as shown by Vary and Schaffer.<sup>11</sup>

Since all of the breakdown reactions of ATP and xanthine are initially reversible, it was hypothesized that by blocking the conversion of xanthine to uric acid through xanthine oxidase inhibition (with allopurinol) a mass action effect would occur effectively retarding the further breakdown of functional nucleotides in the ischemic myocardium. This would preserve the purine bases for subsequent rebuilding when the oxygen supply to the ischemic area was improved. Allopurinol also has vasodilatory effects,<sup>12</sup> and it was felt that this property of the drug may also

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restoring favorable oxygen conditions through enhancement of collateral blood flow to the ischemic area

The present study was undertaken to determine whether allopurinol will reduce the volume of ischemic myocardium in acute open chest experiments on dogs whose mid left anterior descending coronary artery (LAD) had been ligated.

## Methods

Adult mongrel dogs of both sexes weighing 18 to 25 kilograms were used for these experiments. The animals were anesthetized with sodium thio-pental (12 mg/kg of body weight). They were intubated and respiration was maintained with a Harvard respirator. After the chest was opened via a left lateral thoracotomy the pericardium was opened and the edges were sutured to the inner chest wall. A Statham electromagnetic flow probe was placed around the ascending aorta to measure cardiac output. Under fluoroscopic control catheters were placed in both the left and right femoral arteries and their tips were advanced into the left ventricle and central aorta respectively to monitor pressures from these sites. Another catheter was advanced via the coronary sinus into the great cardiac vein for the withdrawal of blood samples. A fourth catheter was placed in the femoral vein for withdrawal of peripheral blood samples. Finally a No. 20 silk suture was placed around the mid left anterior descending coronary artery below the septal and first diagonal branches for subsequent ligation.

To observe the effect of allopurinol on the ischemic myocardium when the drug was administered either orally or intravenously both prior to and following ligation of the LAD the dogs were randomly divided into four groups.

1 Control Group (13 dogs) No drug intervention either before or after ligation of the mid LAD.

2 Post Ligation Allopurinol Treated Group (12 dogs) A continuous intravenous drip of sodium allopurinol was started approximately 20 seconds after ligating the mid LAD and administered at a rate of 16 mg/minute for the entire two hour post ligation period.

3 Pre Ligation Allopurinol Orally Treated Group (six dogs) 400 mg Zyluprim (sodium allopurinol) was administered orally per day for five

days prior to experiments. In addition continuous intravenous drip of allopurinol was started in this group approximately 20 seconds after ligating the mid LAD and was continued through the two hour post ligation period at a rate of 16 mg/minute (as in Group 2).

4 Pre Ligation Allopurinol Intravenous Treated Group (six dogs) Continuous intravenous drip of allopurinol was started approximately 90 minutes prior to ligating the LAD and was continued through the two hour post ligation period at a rate of 10 mg/minute.

With the exception of the three different drug intervention regimes the same protocol was used for all experiments and the following measurements were obtained.

**Hemodynamic** Heart rate, mean central aortic pressure, left ventricular systolic pressure, left ventricular end diastolic pressure, left ventricular  $dP/dt$  (electronically derived), cardiac output and total peripheral resistance (mathematically derived).

**Biochemical** Electrolytes (Na, K, Cl, Ca, Mg), total creatine phosphokinase, free fatty acids, glucose, serum uric acid, total inorganic phosphates, lactate and pyruvates were obtained in arterial blood from the base of the aorta.

Prior to ligation of the mid LAD baseline hemodynamic recordings were obtained and blood samples were drawn for biochemical measurements. Following ligation the same hemodynamic and biochemical variables were recorded and samples at 30 seconds, 5 minutes, 30 minutes, 1 hour and 2 hours post ligation. After obtaining the two hour recordings and samples fluorescein dye was injected into the left ventricle via the LV catheter with the heart beating in situ. This caused unaffected portions of the myocardium to be perfused with the dye and the nonperfused (ischemic) areas to remain free of dye. The heart was then arrested with an injection of 20 mEq KCl into the left ventricle (approximately one minute after the fluorescein injection). The heart was immediately excised, quick frozen in liquid nitrogen ( $-40^{\circ}\text{C}$ ), freeze dried and cross sectioned from apex to base. Subsequent viewing of the cross sections under ultraviolet light clearly defined the perfused (dye stained) areas as greenish gold in color. The nonperfused areas of the myocardium appeared dark blue. Planimetry was then used to measure the nonperfused areas seen

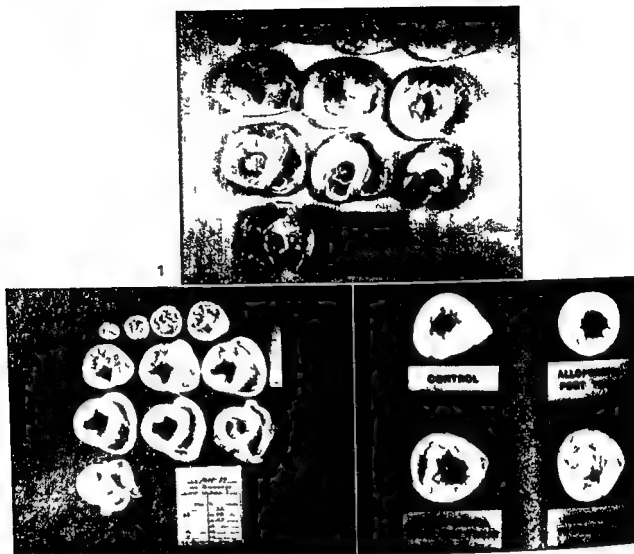


Fig 1 Control heart stained with fluorescein dye freeze dried and serially cross sectioned apex to base. Light green areas (fluorescein stain) are normally perfused areas. Dark blue areas are nonstained ischemic areas. Not large anterior and apical areas of nonperfusion. Some perfusion of immediate subepicardial zone is present.  
 Fig 2 Allopunnol intravenously pretreated heart prepared in same manner as control heart in Fig 1. Note the smaller patchy diffuse areas of ischemia (nonstained blue areas).  
 Fig 3 Comparison of fluorescein dye staining of a single heart section from each of four groups studied. Each section taken from approximately the same level of each heart (1.4 cm. from apex).

on the surface of each section. When this was combined with the thickness of the section, the volume of the ischemic myocardium could be calculated.

#### Statistical analysis

All hemodynamic, biochemical, and tissue data obtained during the study were analyzed for derivation of mean values, standard deviations, and standard errors. Subsequently, two-tailed Student's *t* test analysis was used to determine the significance of any within-group and between-

group differences. In addition, the stain-section measurement data of ischemic myocardium subjected to a one-way analysis of variance, multiple range test for significance of differences.

#### Results

Thirty-seven successful experiments were completed in which meaningful data were obtained. An experiment was considered successful if the animal maintained a stable hemodynamic and biochemical state during the surgical

Table I Calculated ischemic volume below mid LAD ligation in terms of percentage of the total myocardium

	Allopurinol IV pretreat (n = 6)	Allopurinol oral pretreat (n = 6)	Control (n = 6)	Allopurinol post treat (n = 6)
mean	12.28	14.19	19.47	21.56
deviation	2.0	5.5	4.1	8.1

y phase of the experiment and survived ligation of the LAD for a sufficient period of time (at least 30 minutes) to obtain sufficient data for analysis. Those dogs which failed to remain hemodynamically stable during the preparatory phase of the experiment were randomly distributed throughout all four groups and hence were not a consequence of the treatment method.

A total of 24 hearts (six from each group) were perfused with fluorescein dye and were prepared in the manner described above for measurement of ischemic size. In all cases the LAD was ligated at its mid point and the areas of ischemic involvement were measured planimetrically from slides of the serially cross sectioned hearts. Fig 1 is an example of a control heart stained with fluorescein dye, sectioned apex to base and viewed under ultraviolet light. Fig 2 displays an allopurinol intravenously pretreated heart prepared in the same manner.

Table I summarizes the ischemic size data in terms of mean percentage of total myocardium affected below the ligation. The mean percentage of myocardium that was ischemic below the ligation as determined by the fluorescein dye technique ranged from 14.19% to 21.56% of the total myocardium below the LAD ligation in the allopurinol oral pretreated control and allopurinol post treated groups respectively. The allopurinol intravenously pretreated group showed the smallest area of ischemic involvement of 12.28%.

Table II summarizes the Student t test analysis of the data in Table I as to the significance of change in the three treated groups compared to the control group. This analysis indicates that only the allopurinol intravenously pretreated group showed a significant decrease in the calculated ischemic volume. The difference represents a 36.74% reduction in ischemic size from the control group ( $p < 0.05$ ). The same data were subjected to a one way analysis of variance which yielded a significant F ratio (5.30, 3.2156,  $p < 0.05$ ). The subsequent multiple range test indicated

Table II Percent difference in ischemic volumes between control and treated groups

	Allopurinol IV pretreat	Allopurinol oral pretreat	Allopurinol post treat
% difference from control	-36.74	-26.91	+11.00
p value	< 0.05	NS	NS

that the allopurinol oral pretreated control and allopurinol post treated groups represent a homogeneous subset (not significantly different). By contrast the same range test indicated that the allopurinol intravenously pretreated group was significantly different (smaller ischemic area) from the other three groups ( $p < 0.05$ ). A graphic presentation of this analysis is shown in Fig 4.

In addition to having a smaller volume of ischemic tissue the allopurinol intravenously pretreated group exhibited a difference in the configuration of the border zones of the ischemic area. Fig 3 displays a single section from a representative heart of each of the four groups studied. This clearly shows that the control and allopurinol post treated hearts have large solid wedge shaped areas of transmural involvement. Both the allopurinol intravenously pretreated and allopurinol orally pretreated hearts show smaller patchy diffuse areas of non transmural involvement with islands of perfused tissue within the involved area. In addition there are numerous fingerlike projections of perfused tissue penetrating the involved area from the periphery.

In a few of the hearts (two) from each group postmortem pressure controlled injections were made of the coronary arteries using a radiopaque barium sulfate mixture. Filling of the coronary artery with this material permitted subsequent radiographic visualization of the coronary artery.

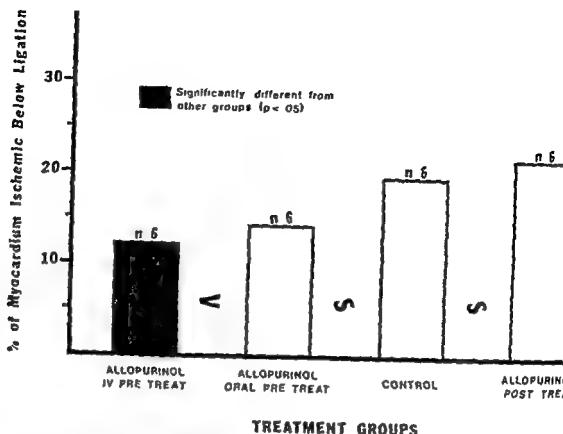


Fig 4 Comparison of mean percentage of ischemic injury of the myocardium below LAD ligation using analysis of variance and Duncan's multiple range test

system and any collaterals when present Fig 5 shows a postmortem coronary angiogram in a control heart which was prepared in the manner described above (heart excised) While the figure presented here is two dimensional the original was a stereo radiograph In both the two and the three dimensional views there was no evidence of open collateral vessels to the distal LAD or its sub branches Fig 6 shows a similar postmortem coronary angiogram on a heart that was pretreated intravenously with allopurinol This radiograph shows (arrows) patent collaterals The obstructed LAD can be clearly seen as can the distal LAD filled retrogradely through collaterals from the distal branches of the circumflex coronary artery

The hemodynamic measurements were done before and continued for two hours after LAD ligation when the dogs were sacrificed for fluorescent dye studies Heart rate was higher at baseline (before ligation) in the allopurinol intravenously pretreated dogs than in controls and remained above control values Early during post ligation there was a decrease in heart rate in all of the

animals but it gradually returned to baseline However the difference between higher heart rate of allopurinol intravenously pretreated and controls persisted although significant only at two hours post ligation (Fig 7) The heart rate of the post ligation animals did not differ from the control

Cardiac output was also higher before in the allopurinol intravenously pretreated dogs than in controls while it was not different from the other groups (Fig 7) Cardiac output decreased in all groups following ligation remained suppressed except for the allopurinol intravenously pretreated dogs in whom it gradually recovered toward baseline The difference however did not reach a level of significance Mean arterial pressure showed a trend to decrease from baseline to a lower level at two hours in both control and allopurinol intravenously pretreated dogs with no significant difference between them Calculated peripheral resistance was significantly lower before in the allopurinol intravenously pretreated dogs while the other groups showed no difference

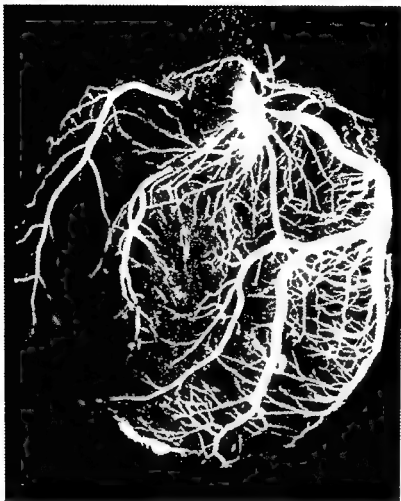


Fig 5 Postmortem radiographic visualization of the coronary artery system in a control experiment. The arrow indicates the abrupt interruption of the filling of the LAD beyond the point of the ligation. Note the lack of filling of the blood vessels beyond this point in the ischemic area.

control (Fig 7). Following ligation there was a gradual increase of total peripheral resistance in all groups then a return toward baseline occurred. In the allopurinol intravenously pretreated animals the resistance was again lower at two hours after ligation than with controls. The left ventricular end diastolic pressure increased moderately in all groups following ligation and then returned toward baseline after two hours with no difference between the control and the treated groups.

Of the 12 biochemical variables measured in arterial blood only three (uric acid, total inorganic phosphates, and calcium) showed significant differences between control and allopurinol intravenously pretreated animals over the two hour post ligation period (Table III). As can be seen in Table III the baseline values for these

variables were also different and remained so for the entire two hour post ligation period. This would indicate that the differences between groups were due to the drug's effect (allopurinol) and ischemia affected the biochemical variables in the same direction but not to a significantly different degree. The other treated groups showed no significant differences in these measurements at baseline and two hours post LAD ligation. Creatinine phosphokinase levels increased but because of prior thoracotomy this cannot be attributed to the ischemic injury alone.

#### Discussion

The present findings indicate that allopurinol when given intravenously prior to ligation of the anterior descending coronary artery will decrease early ischemic injury (two hours after ligation) by





Fig. 6 Postmortem radiographic visualization of the coronary artery system in an allopurinol pretreated dog. Arrow 1 indicates LAD filling at the point of ligation. Arrow 2 indicates retrograde filling of the LAD stump through collaterals from the circumflex artery. Arrow 3 indicates posterior descending branch of the circumflex coronary artery. Note numerous small collaterals in the ischemic area (originally much more numerous when observed under direct vision but partially extracted by freeze drying to obtain the photograph).

36% when compared to control experiments. This difference was significant to the  $p < 0.05$  level. The fluorescein injection technique appeared to be a reliable indicator of nonperfused ischemic areas of the myocardium. As seen in Fig. 3 the control animals (and allopurinol post ligation treated animals) showed solid edge shaped areas of transmural absence of flow while in the allopurinol pretreated hearts there were only small patchy nontransmural areas of no flow with numerous fingerlike projections of perfused tissue penetrating into the nonperfused areas. This suggests partial perfusion in the pretreated hearts from the peripheral border zones. The islands of perfused areas appear to be projections of per-

fused areas from the epicardial zones when they are turned perpendicular to the cross section of the viewed area.

This difference between control and allopurinol pretreated hearts indicates that blood flow is partially maintained in the ischemic area in allopurinol pretreated animals. This is probably due to a vasodilatory action of allopurinol opening up collateral blood vessels. Such coronary (and general) vasodilatory effects have previously been demonstrated.<sup>11</sup> Since allopurinol post treated hearts did not show this partially maintained circulation it must be inferred that the drug must be present in the coronary vasculature prior to the onset of ischemia in order to be effective.

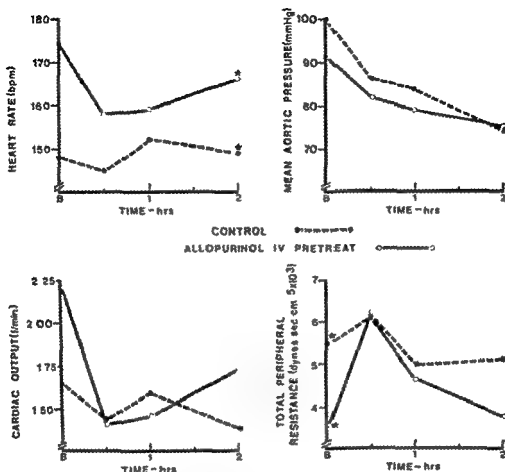


Fig 7 Changes in heart rate mean blood pressure cardiac output and calculated peripheral resistance from baseline values to two hours post LAD ligation. Asterisks indicate significant differences with  $p$  values  $< 0.05$ .

Table III Biochemical changes in arterial blood before and after ligation of LAD

	Baseline	30 minutes	1 hour	2 hours
<i>Uric acid</i>				
Control	$0.93 \pm 0.46$	$1.13 \pm 0.56$	$1.09 \pm 0.55$	$1.19 \pm 0.73$
Allopurinol	$0.33 \pm 0.13$	$0.45 \pm 0.13$	$0.50 \pm 0.05$	$0.46 \pm 0.10$
<i>Total inorganic phosphates</i>				
Control	$4.38 \pm 1.20$	$4.30 \pm 1.20$	$4.62 \pm 1.20$	$4.88 \pm 1.30$
Allopurinol	$2.32 \pm 0.86$	$2.37 \pm 0.83$	$2.44 \pm 0.71$	$3.04 \pm 0.82$
<i>Total CPK</i>				
Control	$76.9 \pm 29.6$	$86.0 \pm 30.8$	$90.17 \pm 30.4$	$106.2 \pm 29.7$
Allopurinol	$81.5 \pm 49.9$	$91.2 \pm 50.8$	$90.8 \pm 53.9$	$110.8 \pm 51.7$
<i>Serum calcium</i>				
Control	$10.39 \pm 2.33$	$10.25 \pm 2.59$	$9.37 \pm 1.71$	$9.38 \pm 1.51$
Allopurinol	$8.48 \pm 0.65$	$8.10 \pm 1.07$	$7.98 \pm 0.67$	$8.18 \pm 0.76$

$p < 0.05$

Evidence for functionally patent collateral blood vessels in the allopurinol pretreated hearts during the LAD ligation was also obtained by the postmortem pressure control injection of the coronary vasculature with a radiopaque BaSO mixture. These injections were obtained by cannulating both the left and right main coronary arteries immediately after sacrificing the animal and excising the heart. Since the injection pressure was monitored and kept at the diastolic pressure the animal had prior to sacrificing we believe this visualization of collaterals is not an artifact caused by an excessively high injection pressure. The difference between the lack of collaterals in the control hearts and the effective collateralization in the allopurinol intravenously pretreated hearts was very impressive (Figs 5 and 6). Other investigators have shown that significant collateral blood flow cannot be demonstrated in the untreated ischemic myocardium of the dog for at least 18 hours after coronary artery occlusion.<sup>1</sup> Also the demarcation of necrotic myocardium from normal is generally extremely sharp and the interdigitation of normal and necrotic tissue is presently only in the borderzone as previously described by Factor and co-workers.<sup>2</sup>

Hemodynamic changes following ligation of the LAD followed the usual pattern of depressed left ventricular function. This consisted of an initial decrease of the heart rate, mean arterial pressure and cardiac output and an increase of the peripheral resistance. After two hours the changes tended to return toward baseline. However in the allopurinol intravenously pretreated animals there was initially higher heart rate, cardiac output and lower peripheral resistance indicating general vasodilation and compensatory increase of cardiac output. The response to LAD ligation was similar to control namely initial decrease of heart rate, blood pressure and cardiac output. There was an eventual return toward the high baseline heart rate and cardiac output and low peripheral resistance in the allopurinol intravenously pretreated dogs. The difference between control and pretreated animals was however statistically significant only for heart rate and peripheral resistance.

The hemodynamic trend indicates that initially there is a depressed left ventricular function following LAD ligation which eventually subsides

or is compensated for. It is probable that the initial depressed function is due to a combination of a mechanical element caused by the contracting ischemic area and to reflex suppression of cardiac function initiated by receptors in the ischemic area itself.<sup>3</sup> It has been shown that the reflexes may overcome attempts by the baroreceptors to compensate for the depressed hemodynamic factors due to the noncontractile ischemic muscle.<sup>4</sup> Apparently however reflex effects are soon compensated for as hemodynamic changes are returning toward control after two hours. Since the animals sacrificed at two hours secondary deterioration of the hemodynamics as often seen in animals followed for longer periods following LAD ligation was not observed.

The changes in the control group during the time period of two hours were only trends and were not statistically significant. However changes in the allopurinol pretreated animals between baseline and 30 minutes as well as between 30 minutes and 2 hours were significant and the differences at baseline and 2 hours between control and allopurinol pretreated animals were also significant. This indicates that reflex suppression probably was very effective in allopurinol intravenously pretreated animals 30 minutes after ligation. That the hemodynamic suppression was reflex in origin is indicated by the rapid return (after 2 hours) to the high levels of baseline cardiac output and low levels of peripheral resistance in the allopurinol intravenously pretreated animals. This baseline and two-hour post-LAD ligation difference seems to be the most significant difference in hemodynamics between the control and the pretreated animals. While these changes are related to the fluorescent angiographic perfusion studies they confirm that a pre-existing systemic (and coronary) vasodilation must be present in the allopurinol intravenously pretreated animals. This is consistent with the finding of partially perfused ischemic areas in the fluorescent studies and the open collaterals in the radiopaque mixture perfusion studies.

The measured biochemical changes obtained from the arterial blood do not contribute significantly to the results. The blood withdrawn was a mixture of blood from the heart and the systemic circulation. The results are therefore nonspecific regarding changes in the ischemic area. Since no

CPK isoenzymes were obtained the CPK levels in open chest animals cannot be evaluated. There was a difference in the uric acid levels at baseline and two hours in the control and allopurinol pretreated animals with the pretreated animals being much lower at both times. This is expected since allopurinol lowers uric acid in the systemic circulation. It is not possible to relate the minimal increases following LAD ligation to any local ischemic metabolic event in the heart muscle. Any protective effect of allopurinol on myocardial nucleotides and purine bases through inhibition of degradation would have to be studied by direct analysis of adenine nucleotides in the ischemic myocardium itself.

It is interesting to speculate on the mechanism of protection of the ischemic myocardium by allopurinol. Allopurinol has been shown to have vasodilatory properties and could have a direct action on the coronary collaterals by keeping them at least in part open when blood flow through the normal channels to a segment of the myocardium is suddenly interrupted. However, it is also possible that allopurinol exerts its effect through prevention of irreversible loss of adenine nucleotides from the mitochondria. Adenosine itself would act locally as a coronary vasodilator. Further investigations are needed to determine the effect of ischemia on mitochondrial nucleotides in the myocardium and also how allopurinol modifies anaerobic metabolism.

### Summary

The effect of allopurinol on the size of ischemic injury was evaluated following ligation of the left anterior descending coronary artery (LAD) in 37 open chest dogs. Heart rate, aortic blood pressure, left ventricular pressure, cardiac output, and total peripheral resistance were continuously monitored. Arterial blood was obtained and analyzed for electrolytes, enzymes, uric acid, total inorganic phosphates, lactate, and pyruvate before and after two hours of LAD ligation. At two hours, the hearts were perfused with fluorescein dye to delineate the flow/no flow areas of the excised cross section myocardium. Planimetry and section thickness were used to calculate the volume of ischemic myocardium.

Heart rate and cardiac output were higher and peripheral resistance was lower at baseline and two hours after ligation in the allopurinol intra-

venously pretreated dogs than in controls. Uric acid was significantly lower at baseline and two hours after LAD ligation and lower levels of total inorganic phosphate, calcium, and magnesium were present at two hours after ligation. The stained cross sectioned hearts showed that the control and postligation allopurinol treated animals had respective ischemic areas of 19.42% and 21.56% of the total myocardium below the section of the LAD ligation obtained perpendicular to the long axis of the heart. In contrast, animals pretreated with allopurinol, whether orally or intravenously, showed 14.19% and 12.28% ischemic areas, respectively. The latter represented 36.74% less ( $p < 0.05$ ) than in the control group. Post mortem angiographic studies performed on hearts from each group demonstrated collateral connections to the distal LAD in the allopurinol intravenously pretreated group and an absence of open collaterals in the control group.

The study suggests that allopurinol pretreatment has a protective effect on the ischemic myocardium. This is probably due to opening of coronary collaterals either by direct vasodilatory action or by maintaining locally high levels of adenosine by enzyme inhibition which in turn acts as a vasodilator.

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## Sudden death in cardiomyopathy Role of bradycardia dependent repolarization changes

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The increased use of portable ECG recorders has permitted observations on the mechanism of sudden death in coronary artery disease. Recent reports have demonstrated ventricular fibrillation as well as sinus arrest preceding death.<sup>1-3</sup> The present report documents changes in cycle length and ectopic activity for 16 hours prior to ventricular fibrillation in a 20 year old patient with cardiomyopathy. Analysis of the relationship of sinus rate coupling interval and corrected QT interval suggests that a unique set of circumstances present for only a brief period may have resulted in ventricular fibrillation (VF).

The results demonstrate the importance of bradycardia-dependent changes in repolarization and illustrate the significance of a post extrasystolic reduction in the prematurity index.

### Case report

A 20-year-old black male was admitted to University Hospital because of cramping abdominal pain of 3 to 4 weeks duration. The patient was allegedly in good health until 1 month prior to admission when he developed weakness and shortness of breath while employed as a construction worker. His dyspnea was accompanied by complaints of nausea, vomiting, and abdominal pain which diminished with meals two weeks prior to admission. An upper gastrointestinal series was said to be normal. One week before admission a chest film as performed by another physician, the patient was advised that his heart was enlarged. The patient continued to complain of epigastric pain and vomiting accompanied by the

development of paroxysmal nocturnal dyspnea and was admitted to the hospital. There was no past history of gastrointestinal or cardiac disease. The patient admitted to the consumption of 6 to 12 cans of beer a day. There was no family history of cardiac disease. Four siblings were said to be in good health.

Physical examination revealed a well-developed male in no acute distress with a temperature of 99.4 F, blood pressure of 120/90 and a pulse of 96 beats/minute. The optic fundi were normal and the thyroid was not enlarged. Examination of the heart demonstrated a regular rhythm. The point of maximum impulse was in the anterior axillary line. An S<sub>1</sub> gallop was present and an S<sub>4</sub> was described by a cardiac consultant. A grade 3/6 systolic murmur along the left sternal border and at the apex was noted. The liver and spleen were not palpable and there was no pretibial edema.

Admission laboratory data included hemoglobin of 15.1 gm%, hematocrit of 45% and white count of 6900. The BUN was 15 mg%, sodium 138 mEq/L, potassium 4.5 mEq/L, total protein 5.3 gm%, albumin 3.1 gm%, bilirubin 1.6 mg%, amylase 95 nephros/dl (normal 70 to 140) and normal urinalysis. A T was 7.3 μg%, ANA negative, VDRL nonreactive, direct Coombs test negative and serum complement (C<sub>3</sub>) 11 mg%.

An electrocardiogram showed normal sinus rhythm with a rate of 81 beats/minute with frequent premature ventricular contractions (PVCs). Voltage criteria for left ventricular hypertrophy and T inversion in Leads I, II, aV<sub>L</sub>, and V through V. The QT interval was 380 msec. and QTc 0.44 second. A PA and lateral chest film showed marked cardiomegaly. An echocardiogram showed a markedly dilated left ventricle (diastolic dimension 9.4 cm) with a calculated ejection fraction of 21%. The mitral valve and aortic valve appeared to be normal. Following admission the patient's rhythm was monitored by telemetry. Maalox was prescribed for abdominal pain. A gastrointestinal work up including a cine esophagram and upper gastrointestinal series with small bowel follow through was normal.

A cardiology consultant made a diagnosis of cardiomyopathy of unknown cause. On the twelfth hospital day frequent multifocal PVCs were noted. A serum digoxin level was 0.95 ng/ml. The patient was moved to the intensive care unit and given intravenous lidocaine with improvement in his ventricular arrhythmia. Oral quinidine 200 mg every 6 hours, was

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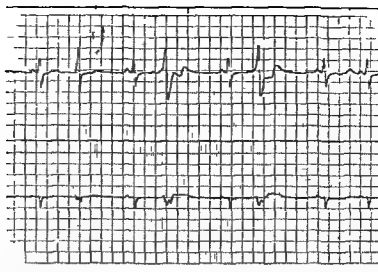


Fig 1 Sequence of PVCs at 2 15 A M. The initial coupling interval was 720 msec. Following the post-extrasystolic pause the coupling interval was reduced to 520 msec for the two following extrasystoles. The cycle length was 840 msec. QT 440 msec. QTc 480 msec.

Table 1 Tabulation of data from Holter monitoring (10 15 A M to 11 00 A M)

	No of PVCs /hr	Heart rate (beats/min)	RR interval (msec)	QTc (seconds)	Coupling interval (msec)	No of PVCs analyzed	Prematurity index	Coupling interval for PVCs
10 A M to 11 A M	75	90.4 ± 3.8	660 ± 39	0.43 ± 0.02	443 ± 25	8	1.28 ± 0.05	480
11 A M to 12 P M	149	90 ± 6.1	655 ± 47	0.44 ± 0.02	460 ± 63	24	1.25 ± 0.21	440
12 P M to 1 P M	174	92.3 ± 8.1	635 ± 56	0.44 ± 0.01	430 ± 40	23	1.27 ± 0.13	440
1 P M to 2 P M	326	89.4 ± 6.1	804 ± 46	0.45 ± 0.03	524 ± 89	35	1.25 ± 0.15	505 ±
2 P M to 3 P M	243	93.2 ± 5.8	610 ± 20	0.43 ± 0.02	444 ± 47	28	1.30 ± 0.16	410 ±
3 P M to 4 P M	73	81.7 ± 6.6	705 ± 40	0.44 ± 0.01	430 ± 38	16	1.18 ± 0.10	443 ±
4 P M to 5 P M	57	90 ± 8.1	649 ± 50	0.44 ± 0.02	441 ± 20	20	1.30 ± 0.11	
5 P M to 6 P M	113	89 ± 7.3	640 ± 60	0.46 ± 0.01	461 ± 80	15	1.25 ± 0.10	
6 P M to 7 P M	164	89.1 ± 9	663 ± 60	0.44 ± 0.01	427 ± 30	35	1.27 ± 0.12	497 ±
7 P M to 8 P M	771	92.4 ± 4.2	629 ± 30	0.43 ± 0.01	431 ± 20	60	1.25 ± 0.08	431 ±
8 P M to 9 P M	332	93.4 ± 6.5	634 ± 45	0.44 ± 0.02	439 ± 50	47	1.29 ± 0.14	471 ±
9 P M to 10 P M	234	78 ± 8.5	768 ± 30	0.48 ± 0.03	581 ± 50	35	1.36 ± 0.11	600
10 P M to 11 P M	29	70.1 ± 3.4	818 ± 30	0.47 ± 0.03	538 ± 0.16	8	1.25 ± 0.29	570 ±
11 P M to 12 P M	42	72 ± 4.4	791 ± 80	0.43 ± 0.01	522 ± 0.09	20	1.39 ± 0.25	460 ±
12 P M to 1 A M	159	68.2 ± 4.9	804 ± 50	0.45 ± 0.03	524 ± 89	35	1.30 ± 0.25	605 ±

initiated on the sixteenth hospital day and given at 9 A M, 3 P M, 9 P M and 3 A M. The final quinidine dose was 11 to 6 hours before death. Digoxin 0.25 mg/day was given from the fifth through the twelfth hospital day. Digoxin was then discontinued on the thirteenth day. No digitalis was given until the seventeenth day when the patient received 0.25 mg orally. On the eighteenth hospital day 0.25 mg digoxin was given orally at 9 A M and 11 P M. The final digoxin dose was given 5 to 6 hours before death.

On the eighteenth hospital day a Holter monitoring was applied at approximately 10 15 A M to follow the progress of his ventricular arrhythmia. Serum electrolytes on the eighteenth hospital day included a serum sodium of 140 mEq/L, potassium 3.9 mEq/L, chloride 97 mEq/L and CO<sub>2</sub> 37

mEq/L. At 2 25 A M on the nineteenth day ventricular fibrillation was noted by telemetry. Cardiopulmonary resuscitation was initiated but was unsuccessful and the patient pronounced dead at approximately 4 00 A M.

At autopsy the heart weighed 610 grams. The left ventricle appeared to be dilated, left ventricular thickness was 1.5 cm. There was no evidence of coronary atherosclerosis or mitral valvular disease. The circumference of the aorta at the level of the arch was 4.5 to 5 cm. Microscopic examination of the myocardium revealed no specific etiology for the cardiomegaly. No inflammatory infiltrate or significant areas of fibrosis were seen. The remainder of the autopsy was noncontributory. No explanation for the patient's gastrointestinal symptoms was found.

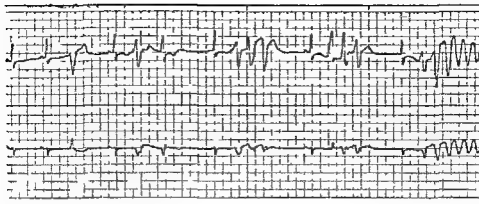


Fig 2 Terminal event at 2 19 A.M. A PVC with a coupling interval of 600 msec is followed by a sinus beat and a PVC at an interval of 460 msec. Paired PVCs result followed by two three beat episodes of ventricular tachycardia. The final extrasystole has a coupling interval of 440 msec and precipitates ventricular fibrillation. Note that there is a tendency for the prematurity index to shorten following the post-extrasystolic pause. The prematurity index for the final seven ectopic beats (first PVC of each sequence) was 1.52, 1.38, 1.36, 1.07, 0.98, and 0.98 respectively. The last ectopic beat with an index of 0.98 initiates ventricular fibrillation. This PVC had the shortest prematurity index observed during the 16-hour period and coincided with a QTc equal to the longest value measured.

Table II Tabulation of data from Holter monitoring (2 15 A.M. to 2 19 A.M.)

	No of PVCs/ min	RR interval (msec)	QTc (sec)	Coupling interval (msec)	No of PVCs analyzed	Prematurity index	Coupling index for paired PVCs/episodes
2 15 A.M.	3	880 $\pm$ 40	0.47 $\pm$ 0.01	587 $\pm$ 115	3	1.33 $\pm$ 0.27	II
2 16 A.M.	1	936 $\pm$ 38	0.46 $\pm$ 0.01	460	1	1.70	0
2 17 A.M.	4	884 $\pm$ 41	0.47 $\pm$ 0.01	740 $\pm$ 167	4	1.64 $\pm$ 0.37	II
2 18 A.M.	1	852 $\pm$ 18	0.47 $\pm$ 0.01	660	1	1.50	II
2 19 A.M.	7	888 $\pm$ 44	0.48 $\pm$ 0.02	531 $\pm$ 99	7	1.19 $\pm$ 0.22	460/1

\*The final sinus beat occurred at approximately 19 minutes and 57 seconds.

### Analysis of Holter recording

Heart rate was measured at 1 minute intervals from a histogram beginning at approximately 10 15 A.M. and extending to the onset of ventricular fibrillation at approximately 11 20 A.M. The number of premature ventricular beats per hour was detected by an automated recording system\*. At 10 minute intervals for the 16 hour period ECG strips of approximately 1 minute duration were obtained. The cycle length and QT interval were obtained from five beats in each sample and the corrected QT intervals (QTc) calculated as the QT interval in seconds divided by the square root of the cycle length in seconds. The coupling interval of all premature ventricular beats was measured in milliseconds as well as the coupling interval of paired ventricular beats and RR

intervals during three consecutive ventricular ectopics. The prematurity index was measured as the coupling interval divided by the QT interval of the preceding sinus beat. All data for the first 16 hours were tabulated at hourly intervals (Table I). During the final hour a continuous recording of the 5 minutes preceding the terminal episode was made. For purposes of this study only the first of a two or three beat sequence was counted in the sample group as a PVC. The coupling intervals of the initial beats are shown in Table I. The automated recording however included all ventricular extrasystoles.

The results are shown in Tables I and II. The total number of ventricular ectopic beats tabulated by the automated recorder was 3 368 from hours 10 00 A.M. until 2 00 A.M. During this period a total of 411 PVCs (13%) were analyzed from sample rhythm strips.



The corrected QT interval did not remain constant over the range of RR intervals shown. There was a significant increase in the QTc at increasing cycle lengths. During the 9 hours with mean sample cycle lengths of less than 680 msec the mean QTc interval exceeded 0.44 second in only one instance (5 to 6 P.M.). The mean QTc interval was greater than 0.44 second in 6 of 8 hours with a cycle length greater than 680 msec ( $p < 0.05$  by Fisher's test). During the 5 minutes immediately preceding death, cycle length ranged from 852 to 936 msec and the QT interval varied from 0.46 to 0.48 second during the minute in which the terminal event occurred. The QTc interval during the final minute was equal to the longest QTc recorded (0.48 second from 10 to 11 P.M.).

Table I demonstrates that ectopic coupling intervals tended to increase at longer cycle lengths so that the prematurity index tended to remain relatively constant from 10:00 to 2:00 A.M. with the exception of 3:00 to 4:00 P.M. when the prematurity index was  $1.18 \pm 0.10$ . During the final minute, however, there was a decrease in the prematurity index to  $1.19 \pm 0.22$  msec for the seven PVCs. Reference to Fig. 2 shows that the prematurity index of the final seven ectopic beats was 1.52, 1.38, 1.36, 1.03, 1.07, 0.98, and 0.98, respectively. The last PVC with an index of 0.98 initiates V.F. The final PVC had both the shortest prematurity index measured during the 16 hours and occurred when the QT interval was equal to the longest value obtained. A reduction in the coupling interval following a post extrasystolic pause is shown in Figs. 1 and 2.

The coupling intervals associated with paired PVCs are shown in the last column of Tables I and II. Not shown are the initial coupling intervals ( $424 \pm 46$  msec) for five episodes of three consecutive ventricular ectopic beats which occurred between 10:00 and 2:00 A.M. (two episodes during hour 7 to 8 and one each during hours 8 to 9, 11 to 12, and 12 to 1).

## Discussion

The occurrence of ventricular fibrillation during the early morning hours of the nineteenth hospital day was unexpected. There was no obvious clinical event which produced the terminal arrhythmia. Ventricular fibrillation developed during a period of limited activity and increased cycle length and was preceded by 4 minutes during which the number of ectopic beats per minute was less than five.

Analysis of cycle length corrected QT interval and prematurity index suggests several factors which may have led to ventricular fibrillation. First the QTc was prolonged (0.48) during the final minute and was equal to the longest QTc interval observed during the previous 16 hours. The association of a prolonged QT interval and increased tendency to ventricular arrhythmias is congenital<sup>1,2</sup> or acquired abnormality<sup>3</sup> is well known, and a recent report has emphasized the value of QTc prolongation as a predictor of sudden death following myocardial infarction. An increased incidence of QTc abnormalities in survivors of out of hospital fibrillation has also been described.<sup>4</sup> The explanation for increased repolarization abnormalities in this patient during longer cycle lengths is unknown. A similar analysis of changes in QTc with cycle lengths in patients with ventricular arrhythmias could not be found.

The prematurity index of the PVC initiating ventricular fibrillation and preceding PVC was less than the index of any PVC observed during the 16-hour period. Although the mean prematurity index from the sample group between 3 and 4 P.M. was  $1.18 \pm 0.10$  msec, the mean QTc interval at that time was considerably less (0.44 second). The combination of a QT interval of 0.48 second and a prematurity index of less than 1 occurred only during the final minute. This unique set of circumstances probably precipitated ventricular fibrillation.

Progressive shortening of the coupling interval following a post extrasystolic pause was observed during the final minute as well as one preceding sequence (Fig. 1). The significance of this phenomenon in human ventricular arrhythmias is unknown, but a reduction in coupling interval may represent a rate related decrease in the conduction time of a reentrant pathway. There was no additional evidence to suggest the presence of parasystolic focus.

The importance of coupling intervals or the R on T phenomenon has been challenged by reports from several investigators.<sup>5-11</sup> These studies have shown that ventricular tachycardia may be initiated from relatively long as well as short coupling intervals. Information obtained by the use of the extrastimulus technique<sup>12</sup> however has shown that a critical range of coupling intervals, whether long or short, is frequently required for the production of ventricular tachycardia. There is insufficient evidence to extend these observations.

ions to the production of ventricular fibrillation it appears reasonable that both a decrease in the fibrillation threshold perhaps produced by repolarization abnormalities<sup>1</sup> and a critical coupling interval may be required.

During the final 3 days of the patient's hospitalization both digoxin and quinidine were administered. Recent studies have shown that serum digoxin levels may be increased in patients given quinidine<sup>18</sup> accompanied by clinical manifestations of digitalis intoxication. Although the mechanism has not been established alterations in digoxin binding have been suggested.<sup>19</sup> The effects of digoxin-quinidine interaction in this patient are unknown. Although serum digoxin levels were not measured during the final 3 days the patient received only three doses of digoxin during this time.

The presence of quinidine intoxication cannot be excluded. Prolongation of the QT interval by quinidine is well known<sup>16</sup> and recent reports emphasize the continuing problem of arrhythmias in patients with quinidine excess.<sup>20</sup> It should be noted that quinidine intoxication might not have been required to produce harmful effects since the QT interval was already prolonged. Additional repolarization changes may have facilitated the occurrence of ventricular arrhythmias.

The patient described in this report was a young man with a history of heavy ethanol intake who presented with abdominal pain and frequent PVCs. In spite of multiple sinus rates and coupling intervals the combination of excessive QT prolongation and prematurity index of less than 1 was found only during 1 minute and was associated with ventricular fibrillation. Analysis of the Holter recording suggests that measurement of QT interval and prematurity index at multiple rates may be required to assess the risk of ventricular arrhythmias in similar instances.

### Summary

A 20 year old man presented with cardiomegaly, frequent PVCs and abdominal pain. On the nineteenth hospital day the patient developed ventricular fibrillation and died. Analysis of a Holter recording initiated 16 hours previously demonstrated an increase in the corrected QT interval (QTc) to 0.48 second and a prematurity index less than 1.0 only during the minute terminated by ventricular fibrillation.

This report documents changes in sinus rate

coupling interval QTc and prematurity index for 16 hours preceding ventricular fibrillation in a patient with cardiomyopathy. The timing of the terminal arrhythmia coincided with significant changes in the QTc and prematurity index characterized by bradycardia dependent QTc prolongation and a post extrasystolic reduction in prematurity index.

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# Spontaneous cure of infected left atrial myxoma following embolization

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The symptoms of cardiac myxoma are varied. Prior to the advent of echocardiography diagnosis was most difficult requiring a high degree of clinical suspicion. We describe a patient with three unusual clinical events: prolonged duration of infected atrial myxoma and disappearance of the echocardiographic findings of myxoma following embolization.

## Case report

The patient is a 51 year-old white female who was admitted to the Baystate Medical Center hospital on August 21, 1977, awakening at night with a severe headache. Disorientation and inability to walk were noted. She had been entirely well until 15 years prior to admission when she sustained a cerebrovascular accident presumed to be embolic. At that time she had been unconscious for one week. It was felt that her embolus was secondary to rheumatic heart disease and the patient was treated with coumadin which was administered continuously until her admission in August 1977. No definite history of rheumatic fever was obtained. In the few months prior to this admission the patient had experienced excessive uterine bleeding. A D & C was performed one month prior to admission. In addition, a few months prior to admission the patient had visited the dentist to have her teeth cleaned. She did not receive endocarditis prophylaxis for either procedure. Over the few months prior to admission the patient complained of increasing fatigue. Physical examination on admission to the hospital revealed a temperature of 101° F. Her eyes were fixed and deviated to the right. She had vertical nystagmus upon lateral gaze. The fundoscopic examination was normal and her neck was stiff. A computerized axial tomographic scan was performed which revealed a left

cerebellar hemorrhage as well as an old left parietal infarct with surrounding secondary atrophic changes. Her hematocrit on admission was 26 and her white blood count was 9,000 with a normal differential. Routine laboratory data were all within normal limits. The electrocardiogram on admission revealed sinus tachycardia but was otherwise normal. Chest x-ray was normal. On August 23 suboccipital craniotomy and drainage of a posterior fossa hematoma was performed. The tissue sent to pathology was reported as showing red thrombus. The patient gradually recovered from her neurological deficits. Three blood cultures drawn on admission, prior to surgery, subsequently yielded *Streptococcus viridans*. The diagnosis of subacute bacterial endocarditis was made and the patient began on intravenous penicillin therapy. On September 10 an echocardiogram was performed which showed multiple echogenic masses behind the anterior leaflet of the mitral valve in diastole (Fig 1A). This was felt to be most consistent with a left atrial myxoma, although the possibility of a thrombus could not be ruled out with certainty. Cardiology consultation was obtained and examination revealed a loud first heart sound, a physiologically split second sound, and a grade II/VI early systolic murmur at the apex. There was no murmur in diastole. The rest of her physical examination was within normal limits. It was felt that following the past course of penicillin therapy an angiographic evaluation of the left atrium should be made. Repeat echocardiogram performed on September 10 and September 21 showed significant change from the original echocardiogram. On October 11 while the patient was awaiting cardiac catheterization she experienced sudden pain and numbness in both legs. There were absent femoral and distal pulses bilaterally. Diagnosis of an aortic saddle embolus was made. She was immediately brought to the operating room where a laparotomy was performed to remove the embolus. Pathologic examination of the embolus revealed "a heterogeneous mixture of material with characteristic features of myxomatous tumor of the type found in the heart. There were nodules of islands of single and multinucleated cells with hyperchromatic nuclei. These cells are surrounded by pools of mucopolysaccharide material. Primitive capillaries in cords of cells are seen" (Fig 2A). Bacterial colonies were noted within the surface consistent with active infection (Fig 2B). On October 14 a repeat echocardiogram was performed which

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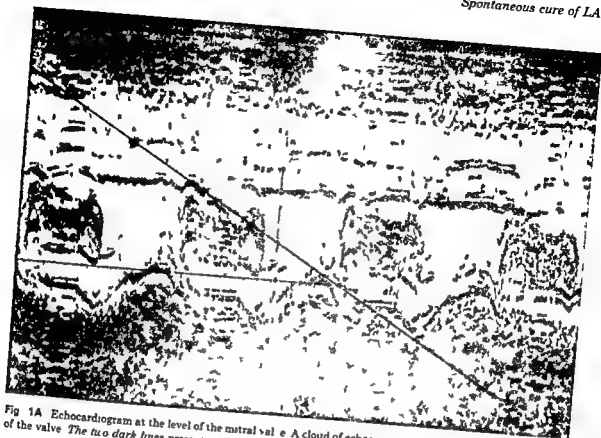


Fig 1A Echocardiogram at the level of the mitral valve. A cloud of echoes is apparent behind the anterior leaflet of the valve. The two dark lines present were drawn to aid in making calculations.



Fig 1B Echocardiogram demonstrating the absence of echoes behind the anterior leaflet of the mitral valve area.

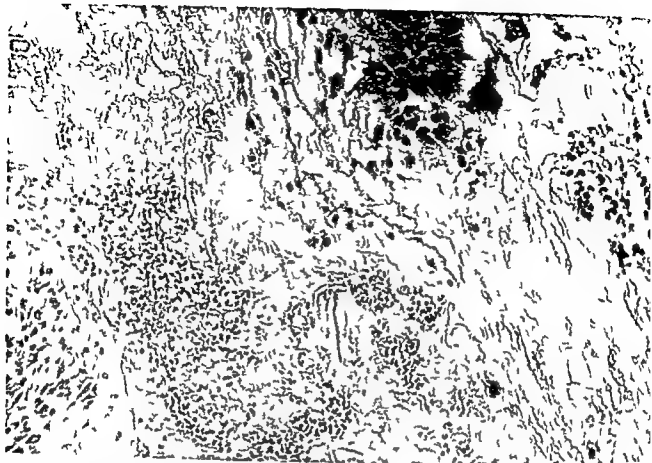


Fig 2A Pathology slide of material removed at laparotomy. There are multiple islands of single and multinucleated cells with hypochromic nuclei. The cells are surrounded by pools of mucopolysaccharide material. Primitive capillaries are seen (Hematoxylin and eosin  $\times 200$ ).

entirely within normal limits (Fig 1B). There were no echoes apparent behind the anterior leaflet of the mitral valve. On October 11 a right-sided catheterization with pulmonary arteriogram and left-sided follow-through was performed. There was no evidence of mass in the left atrium. Multiple repeat blood cultures were negative. The patient remained asymptomatic on no therapy and was discharged from the hospital November 1, 1977, in good condition with no symptoms referable to her cerebellar hemorrhage or saddle embolus. Her most recent evaluation eight months after discharge was unremarkable. Repeat echocardiogram showed no evidence of myxoma.

## Discussion

Our patient had done extremely well following a cerebral embolus 15 years previously. Since she does not have valvular heart disease nor any other known predisposing factors towards premature cerebrovascular disease, it seems likely that her original cerebrovascular accident was secondary to emboli from the myxoma. Most reports indicate that left atrial myxoma is associated with progression of symptoms within two to three

years.<sup>1</sup> However, Goodwin<sup>1</sup> had one patient in his series with symptoms for 15 years. Aland and Greenwood<sup>2</sup> in their series of 31 patients with myxoma described one patient with symptoms for 20 years. Levine<sup>3</sup> discussed a patient with right atrial myxoma which presumably had been present for 28 years. Our patient, as well as appears to have had her left atrial myxoma for a prolonged period of time.

There have been five previous reports of infected atrial myxoma documented by positive blood cultures and organisms in the myxoma. Only three of these were diagnosed antemortem and only two patients survived. Four patients sustained cerebral emboli. In three of the patients the embolic episodes were associated with the infection, although this was the immediate cause of death in only one. One patient had *Staphylococcus aureus* bacteremia which was treated with antibiotics and developed a superinfection with *Candida parapsilosis* which was cultured

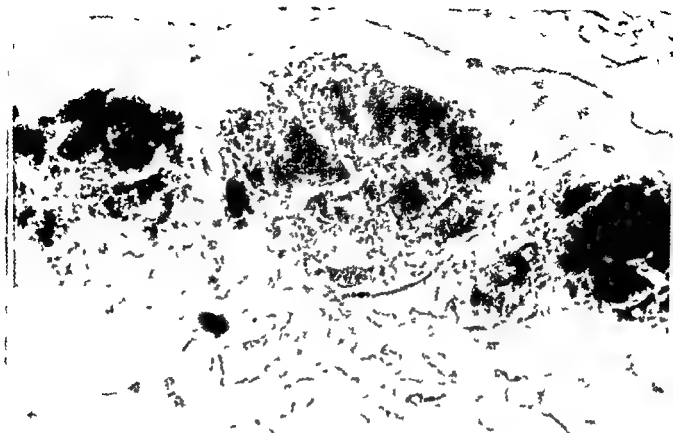


Fig 20 Bacterial colonies noted on the surface of the myxoma (Hematoxylin and eosin, original magnification  $\times 420$ )

from the blood and from the myxoma at postmortem. The second patient developed *Streptococcus faecalis* bacteremia and died from a mesenteric embolus two weeks after sustaining a cerebral embolus.<sup>4</sup> A third patient had been admitted to the hospital with fever and confusion. Blood cultures yielded *Staphylococcus aureus* and an echocardiogram showed a left atrial myxoma. This patient sustained a cerebral embolus and died. The first reported surviving patient was a 50 year old female who was admitted with fever and disorientation. Three blood cultures were positive for *Staphylococcus albus* and one for *Streptococcus viridans*. On physical examination she had signs suggestive of cerebral emboli as well as an intermittent diastolic murmur. The levophase of pulmonary angiography demonstrated a pedunculated mass moving between the atrium and ventricle. Because of the recent embolic episode it was felt that immediate surgery was indicated despite the bacteremia. An atrial myxoma was removed and *Streptococcus viridans* was

cultured from the myxoma. The patient was alive and well 8 months after surgery.<sup>5</sup> Recently a 48 year old woman had an atrial myxoma removed surgically and was found to have hyphal forms typical of *Histoplasma capsulatum* on a thrombus superimposed on the myxoma. Fungal cultures of bone marrow, blood, and pericardial fluid grew *Histoplasma capsulatum*. The patient was subsequently treated with amphotericin B and steroids and was discharged 60 days following surgery. Thus including our patient there have been six cases of infection associated with a left atrial myxoma. Four of the six had embolic episodes associated with the active infection. Three of the six survived two following surgery during the active stage of infection and our patient after successful removal of the saddle embolus.

Embohc complications of myxomas are common, ranging from 33% to 48% in three large series.<sup>1,2,6</sup> Although the embolic material generally consists of tumor fragments or thrombus

from the tumor surface large emboli have been reported.<sup>9,11</sup> Selzer and associates<sup>10</sup> discussed the case of a 51 year old woman with a murmur of mitral stenosis which disappeared following aortic saddle embolus. Eighteen months later congestive symptoms occurred and a diastolic murmur was again heard. Angiography showed a left atrial mass and the myxoma was subsequently removed surgically. Carter and colleagues<sup>11</sup> described a 60 year old female who sustained an aortic saddle embolus. The material removed surgically was a typical myxoma. The patient had no diastolic murmur and an angiogram via an antecubital vein demonstrated no filling defect.

Both echocardiography and the levophase of pulmonary angiography in our patient demonstrated no mass although a small fragment of residual stalk would not be detected by these tests. It is conceivable that her infection caused the severance of the stalk of the myxoma and it is certainly possible that a residual portion of the stalk was retained. Most myxomas arise from the atrial septum near the fossa ovalis and are pedunculated. The other known survivors of an infected myxoma had the myxoma removed during the active stage of infection. Therefore it seems advisable to recommend surgery despite active infection in an attempt to prevent a catastrophic embolization. Our patient sustained such an embolus after consideration of surgery had been postponed until the active course of antibiotic therapy for endocarditis could be complete. Fortunately she recovered. Since atrial myxomas are known to recur after surgery<sup>9</sup> and in spite of the possibility of residual myxoma we have decided to follow our patient with serial examinations and echocardiograms.

We have shown the sequential disappearance demonstrated echocardiographically of a left atrial myxoma. Certainly all patients with or without bacteremia who systematically embolize without predisposing factors deserve echocardiography. Additionally a negative echocardiogram does not rule out the previous presence of the myxoma and in certain situations for example

unexplained embolization repeat echocardiography is probably indicated.

## Summary

A patient with prolonged duration bacterial infection and echocardiographic disappearance of an atrial myxoma following embolization is discussed. Following aortic saddle embolus, echocardiographic manifestations of the patient's left atrial myxoma disappeared. Previous case reports of infected atrial myxomas are reviewed. The necessity of early surgical intervention despite active infection is discussed.

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## Rheumatic fever in children

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*Eia Eia with rising fever  
What does your work up show?  
Is there arthritis?  
A touch of St Vitus?  
How high is your ASO?  
The sounds I hear I fear my dear  
Mark regurgitant flow  
But Jones criteria  
Have yet to appear in ya  
So you're still an F U O*

Anonymous Medical Student 1964

Is rheumatic fever worth the trouble? For almost four decades now we have been offered a steady diet of obituary notices of this disease. If one looks at the widely quoted Danish data (Fig 1) the first impression is that the rheumatic fever incidence has been falling so precipitously that it must surely have gone through the floor by now.

But most children don't live in Denmark. In fact four fifths of the children living today are said to be living in the poverty stricken Third World. The news we get from there are fragments at best but the impression is that of a *déjà vu* with Carlo and Luma reenacting the rheumatic fever scene of Boston and New York in the 1920s. It is not therefore only out of a perverse love of the esoteric and the untimely that we present this review of rheumatic fever in children.

### Epidemiology

The decreasing incidence of rheumatic fever (RF) and rheumatic heart disease (RHD) in the

so called Western world (which includes of course Japan) has become an axiom which meets the consensus of the pediatrician, the cardiologist and the epidemiologist. The number of hospitalized cases of RF is declining, the disease is becoming milder, the Jones criteria have been made more exacting and the identification of non-rheumatic cardiac diseases mimicking RHD has become more frequent. Migrations, urbanization, industrialization and the advent of antibiotics have changed the environment and the host and thereby altered the natural (or perhaps now unnatural?) history of the disease.

**Morbidity and mortality.** In Scandinavian countries the reported incidence of RF has dropped drastically over a century from 200 to 11/100,000 (see Fig 1). In the U.S. the annual incidence of RF in Connecticut hospitals decreased from 12.3 in the period 1934-1938 to 2.9/100,000 in the period 1968-1972<sup>1</sup> and in Nashville from 14.8 in 1964 to 6.4/100,000 in 1969.<sup>2</sup> The annual rate in Baltimore decreased from 40 in 1935 to 23/100,000 in the period 1960-1964 in the age group 5 to 19; interestingly the decline was accounted for mainly by a decrease of recurrences (Fig 2).

A look at the crude death rates from RF and RHD in the U.S. shows a reduction from 14.5 to 6.8/100,000 in the period 1950 to 1972.<sup>3</sup> The age specific death rates indicate that the greatest decline occurred among the young who may have benefited the most from the advent of antibiotics (see Table I).

**Medical care as an environmental factor.** Among the changing environmental factors is the availability of medical care. In the districts of Baltimore serviced by comprehensive care programs (children and youth programs) the incidence of RF declined 60% while it remained

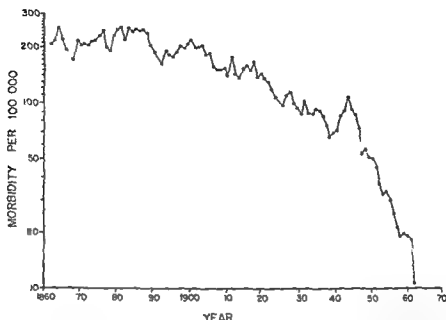
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## REPORTED RHEUMATIC FEVER INCIDENCE IN DENMARK 1862 - 1962



SOURCE: PUBLIC HEALTH BOARD OF DENMARK, COPENHAGEN, DENMARK

Fig 1 Decline in rheumatic fever incidence in Denmark 1862 to 1962. Redrawn as semi log plot from Venderborg F, Faverholdt L and Olesen K H. Decreasing incidence of a history of acute rheumatic fever in chronic rheumatic heart disease. *Cardiologia* 33:332, 1968. Reproduced with permission.

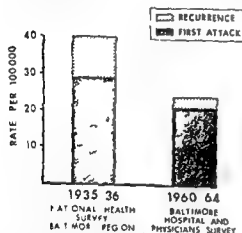


Fig 2 Decline of the incidence of rheumatic fever in the Baltimore hospitals. From Markowitz and Gordis. *Rheumatic Fever*. Philadelphia 1972. W B Saunders Company. Reproduced by permission.

unchanged or increased in the rest of the city. The decline occurred only among the subpopulation of patients with previous sore throat, which is the signal for initiating antistreptococcal therapy and not in the other subset of rheumatic fever patients who had no sore throat prior to the rheumatic fever attack and therefore could not have been helped by the availability of care (see Fig 3). Thus, whether medical care is available

Table 1 Age specific death rates from rheumatic fever and rheumatic heart disease in the US

Age group (yr)	Deaths per 100 000		Decline (%)
	1950	1972	
<24	2.81	0.75	81
25-44	11.35	2.71	6
45-64	27.33	13.92	50
>64	54.53	31.48	41

From Mortimer E A. Control of rheumatic fever: How are we doing? (Editorial). *JAMA* 237:1720, 1977. Reproduced with permission.

and accessible makes indeed a difference. Changes independent of medical care. On the other hand, rheumatic fever started to decline before the introduction of antibiotics (see Fig 1). Other factors are believed to have played a role, such as improved socioeconomic conditions and especially housing (less crowding). In the U.S.A., living space has been increasing steadily even among the poor until recently, although from 1974 to 1976 apartments have been getting smaller (6½ square feet nationwide) and many people have been living in apartments.

Streptococcal changes. The decline in RF incidence may also be explained with a change in

streptococci themselves Quinn and Federspiel<sup>9</sup> demonstrated a decrease in the percentage of Group A streptococci among the beta hemolytic streptococci isolated from the throat of Nashville children from 84% in the period 1953 to 55 to 62.6% in the period 1961 to 67 and a drop in the percentage of typable strains among the Group A streptococci from 51.2% to 17% in the same period (but this could be due to the advent of new M types for which no typing sera were available<sup>9</sup>).

By contrast evolutionary changes in the streptococcus and/or human immunity can be responsible for increased incidence of RF as in the Ryukyu Islands where an outbreak of the disease occurred in 1973 the year of their reversion from USA to Japan. This political change brought in tourism and with it new dominant serotypes to which the natives were not immune<sup>9</sup>.

#### Rheumatic fever in developing countries

Exposure of immigrants to unfamiliar serotypes rampant urbanization and rapid increase in schools might explain the apparently increasing incidence of RF in many developing countries<sup>9</sup>. Another fraction of this increase may be artificial and due to increased awareness of the disease less competition for attention from decreasing communicable diseases and more attention to the health of the natives after independence or during the struggle for it. Thus progress has many components with different in fact often opposite effects on rheumatic fever incidence (Fig 4).

Typical of these developing localities is Soweto the black township on the outskirts of Johannesburg where a careful recent epidemiologic study revealed a prevalence rate of RHD among school children of 6.9/1000 with a peak rate of 19.2 per 1000 children in the seventh grade one of the highest recorded reliably in recent times<sup>10</sup>. The highest reported mortality rate in the world for RHD (27.5/100 000) and one of the highest for ARF (1.0/100 000) are in Egypt whose capital lodges 1/4 of the total country population in conditions of extreme crowding and where rheumatic fever is frequent. By contrast in the Egyptian countryside rheumatic fever is comparatively rare despite the prevailing poverty<sup>1</sup>.

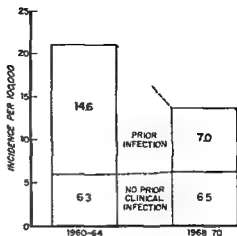


Fig 3 Declining incidence of first attack of rheumatic fever in patients with previous sore throat. From Gordis L. Effectiveness of comprehensive care programs in preventing rheumatic fever. *N Engl J Med* 289:331, 1973.

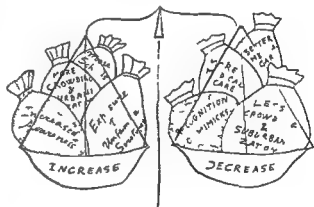


Fig 4 Factors affecting the incidence of rheumatic fever in the western world and "developing" countries.

**Rheumatic heart disease and juvenile mitral stenosis in developing countries.** Rheumatic heart disease is the most common form of heart disease in tropical countries. In Bangkok it affects 39% of all patients hospitalized for heart disease<sup>11</sup> and a recent review in Thailand reports a very high incidence of carditis and of juvenile tight mitral stenosis, the latter attributed to the early onset of subclinical chronic valvulitis or to the frequency of recurrences in the young age group or to both<sup>1</sup>. A high incidence of rheumatic fever at a very young age has been reported in other tropical countries. D'Arbela and colleagues<sup>12</sup> found a peak incidence of the disease in the 6 to 10 year age group followed by the 11 to 15 year age

Developing is a useful thinking kind of word as many develop. We prefer the term 'poor' which is what is usually meant but use the two terms interchangeably.

group with 10% of the total cases in the 0 to 5 year age group (in Kampala, Uganda). This finding is consistent with the higher ASO levels in young children reported from the same hospital.<sup>12</sup> Similar data were collected in East Nigeria in Khartoum and in Pakistan indicating earlier exposure to streptococci and earlier occurrence of most streptococcal diseases in these regions.<sup>14</sup>

Is juvenile mitral stenosis a true variant of rheumatic heart disease? If so is it a variant occurring specifically in tropical or underdeveloped countries? The answer to both these questions remains unknown. The data purporting to show a difference in the incidence of tight mitral stenosis in the young are hospital statistics with an uncertain denominator. Moreover in some series it is not clear whether mitral regurgitation is separated from mitral stenosis and whether congenital lesions are distinct from rheumatic.<sup>15</sup> And certainly in a population where most people are very young as is true in many tropical and developing countries the chances of observing diseases in children by necessity increase. So does the chance of observing a rare manifestation of such diseases. However to the best of our knowledge tight mitral stenosis is never a common lesion in children in the Western world even when rheumatic fever is rampant. Only 1.3% of 1,000 communitarian patients reported by a New York surgeon in 1954 were patients under 20.<sup>16</sup> By contrast 24 of 373 commissurotomy reported by a Vellore South Indian group in 1964<sup>17</sup> were on patients of the same age and similar reports abound.

It is often stated that only 50% of the patients with premature mitral stenosis have Aschoff bodies at surgery or autopsy. It is also reported that only one third to one half of these children have a history of rheumatic fever and that this history is often atypical. How do these clinical findings correlate with the pathologic ones? Can one identify through this correlation a cluster of rheumatic and another cluster of non-rheumatic patients? (Similar questions can be asked of mature mitral stenosis in the West.) Obviously a lot remains to be learned and almost everything remains to be explained about this obscure and important disease.

#### Biologic aspects

Conventional wisdom holds that rheumatic fever if it is a problem at all is a problem of

technology rather than science of development rather than research applied not basic not biologic. A fresh look at the evidence may persuade the reader that rheumatic fever is fully understood as it is often thought to be.

**Surface structure of the streptococcus.** The surface components of pathogenic organisms in general and of group A streptococci in particular have been the object of increasing investigative attention. These components stick to the host's mucosal cells if an attachment beachhead is to be established. They also contain antigenic determinants that must be recognized as foreign and they should be hard to kill by phagocytosis and to be resisted.

Which are the structures that underlie these functions? Going from the outside in we may not find a capsule of hyaluronic acid (a frequent in epidemic strains).<sup>18</sup> Since streptococcal hyaluronic acid is identical with human connective tissues it cannot be recognized as foreign and therefore does not elicit an antibody response. Probably because of its slimy property the hyaluronic acid capsule hinders phagocytosis. Under the capsule if one may or may not be found fibrinase, non-flagella which correlate with virulence.<sup>19</sup> Fimbriae rest two substances lipoteichoic acid and M protein each favoring virulence in its own fashion.

Lipoteichoic acid sticks to epithelial cells exposing epithelial cells from the human mucosa to lipoteichoic acid in solution. After later attachment of streptococci penetrate because binding sites or receptors on the surface of the epithelial cells become saturated with lipoteichoic acid in solution and therefore cannot bind any more with the lipoteichoic acid or fimbriae.<sup>20</sup>

The other virulence factor located in fimbriae is M protein or better the M proteins which form the basis for the prevailing system of classification of group A streptococci into types. These proteins interfere with phagocytosis and antibodies against them overcome the interference. Because there are more than 60 M proteins usually one in each virulent strain the immunity to streptococcal infections is limited to members of the same type sharing the same M protein though a few exceptions are known.

Stimulated largely by the hope of developing an antistreptococcal vaccine much work has

Table II Cross reactions between streptococci and human tissues

<i>Streptococcal component</i>	<i>Human component</i>	<i>Authors (year)</i>
Like protein in cell wall of some group A strains	Myocardium	Kaplan & Meysen (1962)
Glycoprotein of cell membrane	Glycoprotein of glomerular basement membrane	Markowitz & Lange (1964) <sup>20</sup>
Antigen of cell membrane	Histocompatibility antigen	Rapaport (1966)
Cell membrane of all group A strains	Myocardial sarcolemma <sup>21</sup>	Zaborskie & Freimer (1966)
Type I streptococcal cells	Myocardial intercalated discs	Lyampert (1966a)
Four distinct antigens in acid extracts of streptococcal cells	Four distinct myocardial antigens	Lyampert (1966b) <sup>22</sup>
Group A polysaccharide	Glycoproteins of heart valves	Goldstein (1967)
Three distinct streptococcal antigens	Three distinct kidney antigens	Helm (1967)
Streptococcal hyaluronic acid	Mammalian hyaluronic acid and protein polysaccharide	Sandson (1968) <sup>23</sup>
Type I M protein	Several H LA antigens	Hirata & Terasaki (1970)
Antigen of cell membrane	Neuronal cytoplasm of caudate and subthalamic nuclei	Husby (1976)

been done on M proteins several of which have been purified. Up to recently even highly purified M protein preparations were associated with a non type specific determinant<sup>24</sup> responsible for delayed hypersensitivity responses. Serum antibody to this non type specific M associated antigen or protein is common in human sera. Fortunately brief digestion with pepsin greatly reduces the non type specific determinants and isoelectric focusing of an alkaline extract of M protein may have a similar effect.<sup>25</sup>

The term M associated protein (MAP) is used by some authors to identify what others call non type specific protein. MAP is present only in strains containing M protein. Three varieties have been described by immunologic and electrofocusing techniques,<sup>26</sup> and high anti MAP titers have been reported in sera of rheumatic fever patients.<sup>27</sup> In addition a type specific serum opacity factor (SOF) has been found in close association with M protein.<sup>28</sup> M protein and SOF appear to be controlled by closely associated genes located in extrachromosomal plasmid(s) or bacteriophage.

The rigid exoskeleton of the streptococcal cell—the cell wall—is made of group A carbohydrate (rhamnose and N acetylglucosamine) and peptidoglycan. While the streptococcal exoskeleton is similar to the rigid cell walls of plant cells the soft cytoplasmic membrane underlying it is similar to the cytoplasmic membrane of mam-

malian cells. It contains an antigen cross reactive with human sarcolemmal membrane of which more in the next section.

**Immunologic cross reactions between streptococcal and human antigens.** Immunological similarities between mammalian hosts and microbial parasites are important from at least two standpoints. They may trick the host into recognizing the microorganisms erroneously as self; the immune response will then be blunted or abolished.<sup>29</sup> They may also elicit the formation of antibodies directed against the microbial products but capable of reacting with some of the host's antigens as well. Immunologically mediated tissue damage may result.

Many immunologic cross reactions have been described between antigens of group A streptococci and those of man (Table II). Which one if any is a mediator of tissue damage remains uncertain.

Among the cross reactive antibodies those against the cell wall polysaccharide of group A streptococci are of special interest because they have been reported to cross react with structural glycoproteins of human heart valves.<sup>3</sup> A critical structure in rheumatic heart disease and also to persist in patients with residual valvular disease but not in those without it.<sup>30</sup> This difference however could not be confirmed in a large series of patients studied with a different method—(quantitative precipitation in gel rather

Table III Rheumatic fever in 56 twin pairs\*

	Concordant pairs	Discordant pairs	Concordance rate (per cent)
15 Monozygotic twin pairs	3 (4)†	13 (12)†	18.7 (25)†
40 Dizygotic pairs	1 (2)†	39 (38)†	2.5 (5)†

Based on data of Taranta, A. Torosdag S. Metrakos J. Jeger W. and Uchida I. Rheumatic fever in monozygotic and dizygotic twins. Proceedings of the Tenth International Congress of Rheumatology. Minerva Medica, Torino 1961, pp. 96-99. Reproduced by permission.  
†Taken into account pairs of questionable concordance.

Table IV Clinical manifestations of rheumatic fever in members of definitely and questionably concordant twin pairs\*

	Monozygotic twins						Dizygotic twins					
	1		2		3†		1		2†			
	A	B	A	B	A	B	A	B	A	B	A	B
Arthritis or arthralgia	+	+	+	+	+	+	+	+	+	+	-	-
Carditis	+	+	+	+	+	+	-	+	+	+	-	+
Chorea	-	-	-	-	-	-	-	-	-	-	+	-
Erythema marginatum	-	-	-	-	-	-	-	+	-	-	-	-

Data of Taranta A. Torosdag S. Metrakos J. Jeger W. and Uchida I. Rheumatic fever in monozygotic and dizygotic twins. Proceedings of the Tenth International Congress of Rheumatology. Minerva Medica, Torino 1961, pp. 96-99. Reproduced by permission.  
†Questionably concordant.  
‡Concordant also for the rare sequel, juvenile mitral stenosis.

radioimmunoassay) " and in subsequent studies with the radioimmunoassay technique the level of group A antibody decreased after valvectomy suggesting that the cause of the sustained antibody response in patients with rheumatic heart disease if it does indeed occur may be the cross reacting valvular tissue itself.

The nature of the group A streptococcal membrane antigen cross-reactive with human heart was reinvestigated recently by absorption of rheumatic fever sera with sarcolemmal sheets and subsequent elution. The antibody so purified was used to follow the purification of the streptococcal membrane antigen which turned out to consist of four distinct polypeptides with molecular weights ranging from 32 000 to 22 000 daltons.

Attempts to demonstrate a state of delayed hypersensitivity against heart antigens in pa-

Table V Estimated relative odds of con of rheumatic manifestations and cardiac

Manifestations	Estimated relative	
	Not adjusted	Adjusted and
Joint involvement	4.82	
Carditis	1.44	
Chorea	†	4
Heart disease	2.34	

From Spagnuolo M. and Taranta A. Similarity in manifestations of rheumatic fever in siblings. N. Engl. J. Med. 1966. Reproduced by permission.  
†The data presented for chorea were already adjusted for

tients with rheumatic fever have yielded results. " In the guinea pig however sensitive to group A streptococcal antigens result acquisition by T lymphocytes of the avian guinea pig myocardial cells in vitro.

Streptococci associated with pharyngitis with impetigo relation of serologic specific streptococcal sequels. Nature is wanting to tell us something by letting rheumatic fever occur after streptococcal infection of the throat but not of the skin. The mechanism is however since streptococcal infections of the skin and those of the throat more than one respect. Not only is the anatomic site different but so are the predominant types (roughly the first 48 M type pharyngitis types and types with higher are skin types) and the immunologic they elicit (lower antistreptolysin response in skin infections).

Some authors have postulated that the oral site may be the critical factor in the events leading to rheumatic fever because of peculiarities of the lymphatic drainage of the throat others that the cutaneous site is critical as an interruption of that chain of inhibition of streptolysin O by skin lipoteichoic acid.

Bisno and co-workers<sup>17</sup> have pointed out that acute rheumatic fever does not occur in Tennessee during the summer when pharyngitis types prevail in throat cultures. It is however whether these skin types which typically colonize the throat actually are pyoderma strains when in the throat associated with rheumatic fever.

Whether all the pharyngeal strains carry the same risk of eliciting rheumatic fever is also uncertain. Rammelkamp's observations<sup>49</sup> indicated a constant risk of approximately 3% which didn't vary from year to year or from strain to strain as long as the strain was capable of causing a definite pharyngitis. But Kuttner and Krumwiede<sup>50</sup> reported that a virulent epidemic of type 4 streptococcal pharyngitis among children with previous rheumatic fever failed completely to elicit recurrences and Widdowson and associates<sup>51</sup> recently presented evidence that production of lipoproteinase opacity factor may be associated with diminished rheumatogenicity. On the basis of these and other observations Stollerman<sup>52</sup> has argued that there are rheumatogenic and non-rheumatogenic strains in analogy with the well established distinction of nephritogenic and non-nephritogenic strains.

**Immunogenetics** If the detailed study of the microorganism fails to reveal why some patients with streptococcal infections develop rheumatic fever and most don't, then a detailed study of the host perhaps will. Monozygotic twins have a higher concordance rate for rheumatic fever than dizygotic twins (Table III) and their clinical manifestations are more concordant also (Table IV).<sup>53</sup> Even in siblings other than twins the similarity of clinical manifestations of rheumatic fever is significantly greater than it would be accounted by chance alone (Table V).<sup>54</sup> All these observations intimate that a host factor probably genetic contributes to determine whether after a streptococcal infection rheumatic fever will appear in any given individual.

Efforts to find a marker for this postulated susceptibility have failed thus far. HLA types which correlate with the susceptibility to many diseases don't seem to correlate consistently with the susceptibility to rheumatic fever.<sup>55, 56</sup> Nevertheless the intriguing observations of an association of immune responsiveness to streptococcal antigens and HLA type<sup>57</sup> and of decreased mixed lymphocyte reactions among rheumatic subjects<sup>58</sup> suggest the potential fertility of the immunogenetic approach.

*Note added in proof:* A novel B cell antigen provisionally named 833 has now been reported in association with hemolytic fever in two distinct populations: 1) patients and with a relative risk of 12.9 (Patarroyo M, Winchester R, Velasco A, Cibulsky A, Chlen F, Zabriskie J B, and Kunkel H G. Association of a particular B cell antigen with susceptibility to rheumatic fever. *Third Annual Meeting of the American Rheumatism Association*, May 30-June 1, 1979).

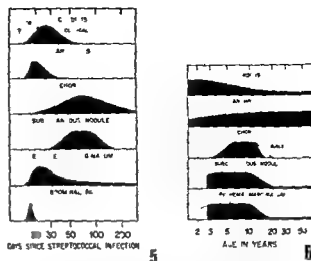


Fig 5 Schematic diagram of the sequence of appearance of the various rheumatic fever manifestations. The maximum height of each curve indicates the time at which most of the cases of a given manifestation appear. The time is represented on a logarithmic scale. From Taranta A. Clinical aspects of rheumatic fever in Arthritis and Allied Conditions 9th ed. J L Hollander and D J McCarty Jr editors Philadelphia 1979 Lea & Febiger. Reproduced by permission.

Fig 6 Schematic diagram of the variations with age of the incidence of the major manifestations of rheumatic fever. The maximum height of each curve indicates the age of maximum incidence. From Taranta A. Clinical aspects of rheumatic fever in Arthritis and Allied Conditions 9th ed. J L Hollander and D J McCarty Jr editors Philadelphia 1979 Lea & Febiger. Reproduced by permission.

### Clinical manifestations

Although arthritis is emphasized in its name RF is not important because of it since arthritis is short lived and leaves no sequel with one questionable exception (see below). Carditis is the most serious manifestation because it is the only one that can cause death during the acute attack, residual disability, and late mortality.

The incidence of the reported clinical manifestations of RF varies according to the age and sex of the patient, the diagnostic criteria used, and the time and place in which the series were collected. Yet series of first attacks studied prospectively and carefully are remarkably similar throughout the world.<sup>59, 60</sup> Recurrences differ in having more frequent and more severe carditis and higher mortality. Many of the differences among RF series stem probably from varying proportions of recurrences to first attacks.

Fig 5 shows the sequence of the appearance of the manifestations and Fig 6 the variations



Fig 7 Erythema marginatum (Courtesy of Dr B F Mas  
April 1957, Mass)

Table VI Jones criteria (revised) for guidance in  
the diagnosis of rheumatic fever\*

Major manifestation	Minor manifestations	
	Clinical	Laboratory
Carditis	Previous rheu- matic fever or rheumatic heart disease	Acute phase re- actions Ery- throcyte sedi- mentation rate
Polychloritis	Arthralgia	C reactive pro- tein leukocytosis
Chorea	Fever	Prolonged P R interval
Erythema marginatum		
Subcutaneous nodules		
<i>Supporting evidence of streptococcal infection</i>		
Increased titer of streptococcal antibodies		
ASO (antistreptolysin O)		
Other antibodies		
Positive throat culture for Group A streptococcus		
Recent scarlet fever		

From Stillerman G H Markowitz M Taranta A Wannamaker  
L W and Wittermore R Jones Criteria (revised) for guidance in the  
diagnosis of rheumatic fever *Circulation* 32:664 1965

with age Arthritis becomes increasingly frequent  
with age while carditis has an opposite trend

Arthritis is exquisitely painful Joints predom-  
inantly the large ones and especially of the lower  
limbs are affected in quick succession each joint  
maximally for only a few days or a week at the  
most so that the arthritis of several joints overlap  
partly in time

If arthritis is not shortened by antinflammatory  
treatment it can last 1 week or in 1/2 of the

cases 2 to 3 weeks Arthritis tends to be of shorter  
duration and to be less severe in children than  
adults\*\*

The arthritis of rheumatic fever has been  
reported to last longer in Scandinavian country  
(up to 1 year)\* which was a finding puzzling  
radiologic joint changes other than soft tissue  
swelling are ever found in rheumatic fever  
after it, with the questionable exception  
*Jaccoud's arthritis* This is characterized  
deformities of the fingers with erosions of  
metacarpal heads resulting in character-  
istic hook like deformities\*\*\* Jaccoud arthritis if  
indeed a sequel of rheumatic fever is an extremely  
rare one

Carditis is diagnosed by characteristic aus-  
cultatory signs such as the apical systolic murmur  
mitral regurgitation which is characteristic  
long occupying most or all of systole (holo-  
systolic), blowing, of relatively high pitch and with  
loudness of at least two but usually three  
more on a scale of six (a corollary of its loudness  
is that it can be heard in the axilla and is  
obliterated by inspiration or changes in posture  
the apical mid diastolic murmur (Carey Coon  
presumably due to 'relative mitral stenosis'  
caused by dilatation of the left ventricle or  
frequently, the basal diastolic murmur of ac-  
regurgitation pericardial friction rubs and  
of CHF, such as cardiomegaly persistent eleva-  
tion of the sleeping pulse rate and gallop  
rhythms Unlike some other cardiopathies  
rheumatic carditis cardiomegaly and heart failure  
do not occur unless accompanied by an organic  
murmur

*Prolongation of the PR interval* can occur  
40% of the patients It is useful in the diagnosis  
rheumatic fever but not in that of chronic  
significant carditis (because it does not correlate  
with organic murmurs) or in prognosis (because  
it does not correlate with residual heart disease)

*Chorea* is the most curious manifestation of  
rheumatic fever It occurs over the most limited  
age range it does not occur under 3 years of age  
and becomes rare again after puberty In adults  
it has been rarely seen and then only in pregnant  
women (chorea gravidarum) it has a familial  
predilection which increases after puberty\*\*

Chorea is also the manifestation with the steepest  
decline in incidence (e.g. from 52% in 1930  
0% in 1975)\*\* in the Western world

Involuntary and purposeless movements of

acing muscular weakness and emotional lability are the symptoms of chorea (popularly "St Vitus dance"). They can occur unaccompanied by the other major manifestations with normal acute phase reactants and low ASO after a latent period longer than that of the other clinical manifestations of RF. The latent period between streptococcal infection and chorea may be as long as several months which makes the connection between the two events difficult indeed to explain.

Patients who develop chorea as an apparently isolated manifestation have a relatively high incidence of RHD in later years (23% after 20 years). Such patients may have had before chorea but after the strep infection that caused it a mild transient carditis which caused no symptoms but sowed the seed of chronic valve disease.

Subcutaneous nodules have a reported incidence between 30 and 2% they are very rare under age 3 and again in adults interestingly they are much more frequent in the presence than in the absence of carditis. They seem to be very rare nowadays.

The nodules of rheumatic fever are smaller and shorter lived (less than 1 month) than those of rheumatoid arthritis the olecranon is the area most frequently involved.

Erythema marginatum (Fig 7) is a non pruritic pink evanescent skin rash which occurs mainly on the trunk the buttocks or the proximal parts of the limbs in the early phase of the attack but may reappear later even during convalescence. As the name suggests individual skin lesions expand centrifugally while the skin in the center returns to normal. It appears only in patients with carditis with an incidence between 10 and 2% (Fig. 7).

Among other rare manifestations abdominal pain can be the earliest. It has been attributed to mesenteric adenitis because Yersiniosis is known to cause abdominal pain as well as arthritis and carditis. One wonders whether these RF attacks heralded by a bellyache might not have been Yersiniosis instead.

### The Jones Criteria and the differential diagnosis of rheumatic fever

As every medical student knows T D Jones divided the manifestations of rheumatic fever into major and minor according to their diagnostic usefulness (Table VI) and proposed

**Table VII Common errors in the diagnosis of rheumatic fever**

1. Failure to use the Jones criteria or incorrect application of them
  - a. Arthralgia mistaken for arthritis
  - b. Day time tachycardia or prolongation of the P R interval mistaken for definite evidence of carditis
  - c. A physiologic systolic murmur made louder by fever and mistaken for a pathologic murmur

*Consequence* A minor illness is misdiagnosed as rheumatic fever and unnecessary therapy and prophylaxis are instituted. The patient affected by cardiac non-disease may become a "cardiac neurotic".
2. Uncritical reliance on the Jones criteria
  - a. Many patients may fulfill the Jones criteria yet have other diseases (rheumatoid arthritis bacterial endocarditis congenital heart disease with congenital failure precipitated by an infection osteomyelitis lupus erythematosus etc.) Evidence of a preceding streptococcal infection will reduce but not eliminate the possibility of these errors.

*Consequence* A major disease is wrongly diagnosed as another major disease. The patient may suffer not only because of the reasons listed under 1 but because treatment of the correct disease is not given.

**Table VIII Auscultatory errors**

### A False positive diagnosis of rheumatic heart disease

Physiologic sounds	Erroneous interpretation
Systolic murmur in pulmonary artery best heard along left sternal border	
a. When audible at apex	Mitral regurgitation
b. When audible in aortic area	Aortic stenosis
Split 1st sound at apex with roughened 1st component and loud 2nd component	Mitral stenosis
Roughened and long 3rd sound at apex without an associated apical systolic murmur	Mitral stenosis or Acute mitral valvulitis
Gallop rhythm mimicking diastolic rumble	Mitral stenosis
Short echo effect after loud 2nd sound at base	Aortic regurgitation

### B False negative diagnosis of no rheumatic heart disease

Pathologic sounds	Error
Short diastolic blowing murmur of aortic regurgitation along left sternal border	a. Not detected
Presystolic rumble of mitral stenosis	b. Detected and tuned as systolic
	Often not detected if patient is not exercised and put in left lateral position



# SITE OF JOINT INVOLVEMENT WITH BACTERIAL ENDOCARDITIS

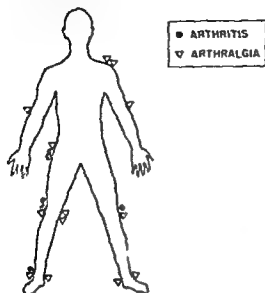


Fig 8 Joint involvement in infective endocarditis in children. Note the similarity to rheumatic fever in the predilection for large joints especially of the lower limbs. From Taranta A. Recent advances in diagnosis and in the prevention of rheumatic fever. Bol Assoc Med P R 69:45 1977. Reproduced by permission.

that the presence of two major or of one major and two minor manifestations indicates a high probability of the presence of rheumatic fever. The criteria have been widely accepted and have proved useful especially in avoiding overdiagnosis. In 1965 they were revised to include a confirmatory role for the preceding streptococcal infection.

What most medical students (and many physicians) do not know is that the Jones Criteria are a guide not a rule: they are not meant to be an exercise in diagnosis by rote or a gimmick to bypass the physician's mind.

A recent review<sup>10</sup> showed that 40% of the rheumatic fever cases reported to the Minnesota Rheumatic Fever Registry did not fulfill the Jones Criteria and may have been overdiagnosed.<sup>11</sup> Fever and arthralgia was the most common presentation of these patients. In fact now that subcutaneous nodules, erythema marginatum, and chorea are rare, overdiagnosis (see Tables VII and VIII) arises predominantly from misinterpretations of the signs and symptoms of arthritis and carditis. Arthralgia is mistaken for arthritis, emotional tachycardia (absent during sleep) and prolongation of the PR interval are

considered evidence of carditis and functional apical systolic murmurs are misinterpreted as organic.

Other and more serious errors may arise from uncritical reliance on the Jones Criteria. Many patients may fulfill them and yet have another disease like juvenile rheumatoid arthritis, congenital heart diseases, systemic lupus erythematosus, or osteomyelitis. One should remember that streptococcal infections are common especially in children and therefore they can often precede an unrelated disease purely by chance. Group A streptococcal arthritis is a frequent cause of acute arthritis in the adolescent; polyarthritis also occurs in preicteric and anicteric viral hepatitis after rubella vaccination. Recently, Lyme arthritis has been described in a cluster of Connecticut children often associated with an erythematous skin rash; it may resemble juvenile rheumatoid arthritis as well as rheumatic fever.<sup>12</sup>

In Scandinavian countries *Yersinia Enterocolitica* is currently a more frequent cause of arthritis and carditis than RF and it has been suggested that at least in those regions *Yersinia* infection must be excluded to make a definitive diagnosis of RF.<sup>13</sup> Carditis has been reported in 27% of cases of *Yersinia* arthritis.<sup>14</sup> However, the descriptive murmurs in most of these cases do not necessarily indicate organic heart lesions. Fever, diarrhea, often present in *Yersinia* arthritis, help in the differentiation.<sup>15</sup>

Viral carditis may mimic rheumatic fever since in addition to pericarditis, cardiomegaly, heart failure, organic sounding murmurs appear. Of 22 cases of viral carditis, eight had apical systolic murmur, three of which pansystolic, and five of which were loud descending systolic murmurs with maximum intensity at the apex.<sup>16</sup> As in the case of juvenile arthritis, streptococcal antibody titers may be in dubious cases, especially if they are consistently negative; if they are positive they may be coincidentally. Hence viral isolation, antigen and viral antibody titers may be worthwhile.

The differential diagnosis of rheumatic carditis includes also infective endocarditis, especially when it presents with arthralgia or arthritis, often does in children. The distribution of affected joints is similar to that of RF (Fig 9). *Atrial myxoma* also can present with cardiac murmurs, arthralgia, elevated ESR, leukocytosis.<sup>17</sup> Among blacks, another source

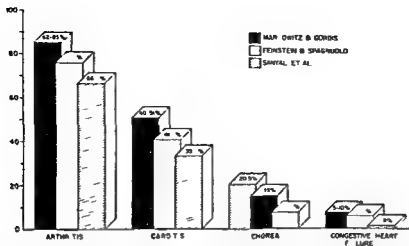


Fig. 9 Similarity of the clinical profiles of the first attack of rheumatic fever in the U.S. (Markowitz and Gordis and Feinstein and Spagnuolo) and Indian groups. From Sanval S. K., Thapar M. K., Ahmed S. H., Hooja V., and Tewari, P. The initial attack of acute rheumatic fever during childhood in North India. A prospective study of the clinical profile. *Circulation* 49:7 1974. Reproduced by permission.

diagnostic confusion involving heart and joints is *sickle cell anemia* which may mimic RF because of heart murmurs and arthralgia but may also of course coexist with it.<sup>33</sup>

As a disease decreases in incidence everything else remaining constant the proportion of false positive diagnoses will increase. This has been reported for tuberculosis<sup>34</sup> and may well be happening now for rheumatic fever in the Western world. To avoid this one needs an ever more critical stance but no more critical perhaps than suggested by T. D. Jones himself 34 years ago. One must constantly search for laboratory and clinical evidence of other diseases.<sup>35</sup>

Are the Jones Criteria inadequate? Diagnostic criteria are perforce arbitrary as they set up a sharp boundary between disease and non-disease while no such thing exists in nature. In the case of rheumatic fever it has been said that the Jones Criteria are not sufficiently sensitive especially perhaps in the developing countries and therefore children who should have this diagnosis do not and may suffer recurrences as a result. On the other hand increasing sensitivity inevitably increases the percentage of false positive diagnosis which also causes suffering.

Some of these problems arise from inappropriate literalness others from incompleteness of observations and data and still others from the dichotomous pattern of medical decision trees. We have no problem with admitting that the boundary between health and disease is fuzzy and submit that pretending that it is sharp is of

no help. If a patient comes to medical attention after receiving therapy or after joint pains subsided spontaneously there is no way to tell arthritis apart from arthralgia. If streptococcal antibodies are not available how can one confirm the preceding infection? But in such cases inability to confirm is fundamentally different from exclusion. The prudent physician will therefore set up a category of questionable diagnoses and use it in a probabilistic manner in decision on therapy and prevention integrating it with the risks and benefits one can foresee from each.

As for the reported geographic differences in the clinical pattern of rheumatic fever and therefore the need for localized Jones Criteria selection biases have never been excluded. In countries where physicians are scarce and hospital beds are at a premium patients with the transient arthritis of rheumatic fever and without heart failure are unlikely to find their way into hospital services. But recent careful prospective studies from India (see Fig. 9)<sup>36</sup> and Trinidad<sup>37</sup> indicate that in these localities at least rheumatic fever does not differ from the garden variety and by implication that the Jones Criteria are valid there also.

The role of the laboratory in the diagnosis of rheumatic fever is mainly confirmatory when it reveals the existence of a recent streptococcal infection and of a systemic inflammatory state. The lack of either throws doubt on the diagnosis (with the exception of isolated chorea and of longstanding carditis). According to the revised

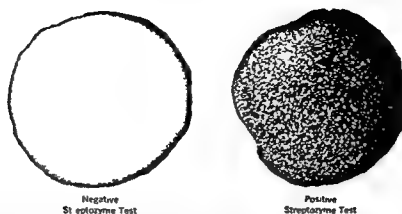


Fig 10 Streptozyme test negative and positive streptococcal passive hemagglutination test. A two minute test, highly sensitive for streptococcal infections. From Janoff J, Janoff D, Taranta A, and Cohen H. A screening test for streptococcal antibodies. *Lab Med* 2:38, 1971. Reproduced by permission.

Table IX Natural history of rheumatic fever

Authors and years of study	No of pts	10 years			20 years		
		Dead of RHD/SBE	No HD	RHD	Dead of RHD/SBE	No HD	RHD
Bland and Jones 1921-31	1 000	202 (20%)	323 (32%)	475 (47%)	301 (30%)	319 (32%)	390 (39%)
Ash 1922-32	537	143 (26%)	203 (38%)	191 (36%)	?	?	?
Cooperative Study 1951-52	497	19 (4%)	292 (59%)	183 (38%)	?	?	?
Irvington House (Estimated) 19>2	599	18 (13%)	400 (67%)	181 (30%)	?	?	?

SBF = subacute bacterial endocarditis

Jones Criteria ASO titers of at least 250 units in adults and 333 in children over five years of age are considered indicative of a recent streptococcal infection.\*

However the ASO titer is elevated only in 70 to 80% of patients with RF; therefore a low ASO titer by itself does not rule out the diagnosis. In recent years the streptozyme test has been used successfully as a second streptococcal antibody test or even as a single test in lieu of the ASO or as a screen before doing the ASO. It is a simple and rapid test which can even be done at the bedside (see Fig 10) and has much to recommend it, although concern lingers over the reproducibility of the reagents from batch to batch.

Another approach to the laboratory diagnosis of rheumatic fever is the determination of heart antibodies. These have been useful in selected cases but have not yet entered general use.

### Recurrences of rheumatic fever and evolution of rheumatic heart disease

Recurrences are a striking feature of RF which set it apart from most other diseases of infectious etiology. Influence markedly the prognosis. RHD and are the target against which prophylactic intervention can be most efficiently directed. The frequency of recurrences in the 60 days and their relative rarity since secondary prophylaxis was introduced in the 1940s is probably the main reason for the change in prognosis of RF in recent years (Table IX).

The same clinical manifestations present in the initial attack of RF tend to reappear preferentially in recurrent attacks (Table X). RF recurrences occur only among those patients who develop streptococcal antibody response and the recurrence rate per infection increases with the magnitude of the antibody rise. At each level

**Table X** Major clinical manifestation of rheumatic fever recurrences according to manifestations of the first attack\*

Manifestations of first attack (isolated or combined with others)	Manifestations of recurrences (isolated or combined with others)		
	Polyarthritis	Carditis	Chorea
Polyarthritis (N = 149)	110 (74%)	81 (34%)	18 (12%)
Carditis (N = 89)	44 (49%)	62 (70%)	2 (2%)
Chorea (N = 68)	11 (16%)	10 (15%)	54 (79%)

Data of Roth, I R Lingg III and Wittemore A. Heart disease in children. A rheumatic group I. Certain aspects of the age at onset and recurrences in 458 cases of juvenile rheumatism ushered in by major clinical manifestations. *AM HEART J* 13:36 1937

**Table XI** Ratio of rheumatic recurrences to streptococcal infections in patients stratified for pre-existing rheumatic heart disease and for ASO rise\*

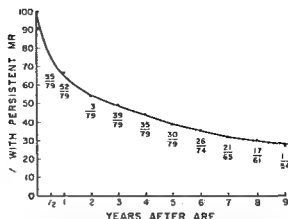
ASO rise in number of tube dilutions	Pre-existing heart disease	No pre-existing heart disease
0-1	3/24 (13%)	1/9 (1%)
2	10/38 (26%)	3/50 (6%)
3	6/16 (38%)	5/34 (15%)
4+	9/16 (56%)	9/26 (35%)

From data of Taranta, A Kleinberg E Feinstein A R Wood H F Turky E and Simpson R. Rheumatic fever in children and adolescents. IV. Relation of the rheumatic fever recurrence rate per streptococcal infection to the titers of streptococcal antibodies. *Ann Intern Med* 80(Suppl 5):47 1964

antibody response streptococcal infections are more likely to lead to recurrences of RF in patients with preexisting rheumatic heart disease than in those without it (Table XI)

It has long been known that the prevalence of RHD increases with the number of previous attacks (Table XII) but this is due to the increased tendency to recurrences in patients with RHD (see again Table XI) rather than to the *de novo* appearance of RHD in patients initially free of it

In the absence of recurrences new valvular lesions do not appear even in patients who had carditis in the initial attack but old valvular lesions may evolve. The severity of RHD at follow up is generally proportional to the severity of the acute carditis. Mitral regurgitation frequently disappears (see Fig 11) but may also



**Fig 11** Persistence and disappearance of mitral regurgitation in patients maintained on continued and effective prophylaxis. Follow up of 79 patients who had mitral regurgitation with their first attack. In the 54 patients still followed at 9 years mitral regurgitation was still present only in 14 out of 54 (26%). From Tompkins, D G Boxerbaum B, and Liebman T. Long term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. *Circulation* 45:543 1972. Reproduced by permission.

**Table XII** Prevalence of rheumatic heart disease according to number of previous attacks of rheumatic fever\*

Previous attacks	Number of patients	Number of patients with heart disease
0	797	264 (33%)
1	280	170 (60%)
2	57	43 (75%)
3	31	25 (81%)
4	4	4 (100%)

Adapted from Taranta, A, Kleinberg E Feinstein, A R, Wood H F Turky E and Simpson R. Rheumatic fever in children and adolescents. IV. Relation of the rheumatic fever recurrence rate per streptococcal infection to the titers of streptococcal antibodies. *Ann Intern Med* 60(Suppl 5):47 1964

worsen. Mitral stenosis may gradually develop. Aortic regurgitation once it becomes symptomatic runs usually a rapid downhill course, and aortic stenosis in combination with regurgitation may slowly appear (by contrast pure aortic stenosis is almost never rheumatic).

What causes the progression of valvular disease in the absence of clinically detectable recurrences is uncertain. The absence of mitral stenosis on follow up of some populations of children maintained on rigid (benzathine penicillin) antirheumatic prophylaxis<sup>23</sup> makes one wonder whether

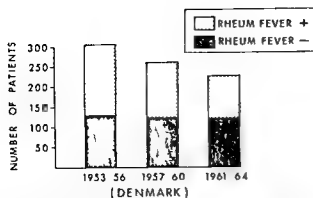


Fig. 12 Incidence of rheumatic heart disease in Denmark with and without a history of acute rheumatic fever. Notice that a decrease occurred only in the group with such history. From Vendsborg P, Faverholdt L and Olesen K H. Decreasing incidence of a history of acute rheumatic fever in chronic rheumatic heart disease. *Cardiologia* 53:332, 1968. Reproduced by permission.

Table XIII Causes of mitral regurgitation in necropsy patients older than 14 years\*

Cause	Number of patients
Rheumatic	30
Rupture of chordae tendineae in previously normal valve	15
Floppy valve	4
Congenital	4
Corrected transposition	1
Partial A-V canal	1
Endocardial fibroelastosis	1
Parachute valve	1
Possible annular calcification	1
Uncertain	1
Total (20 males, 30 females)	55

\*From Ilberts W and Perloff J H. A clinicopathologic survey of the condition causing the mitral valve to function abnormally. *Ann Intern Med* 77:920, 1972.

clinical or subclinical recurrences might be necessary for the development of mitral stenosis. Alternatively or adjunctively the altered blood flow pattern caused by the initial lesion may alter the valve further in a slow vicious circle.

#### Valvular heart disease and its differential diagnosis

More than 50% of patients with valvular heart disease of the kind traditionally considered rheumatic deny any history of RF attacks. It was formerly assumed that all of these patients had had an attack of isolated, silent rheumatic carditis

that is carditis without symptoms of heart failure or of pericarditis and therefore undiagnosed. While this scenario is clearly possible, it must account for a fraction of such patients; other etiologies occur also and are being recognized with increasing frequency.

In the young the differential diagnosis with congenital malformations is mandatory in western countries: the ratio of congenital heart disease to RHD in college students is 4:1<sup>98</sup> and the majority of children undergoing mitral valve replacement have congenital heart disease<sup>99</sup> (India by contrast 77% of such patients have RHD).<sup>97</sup> In a review of 55 cases of mitral disease in infants (an age group of course immune for rheumatic fever) 29 had primary malformation of the valve and 26 had mitral valve dysfunction due to papillary muscle infarction consequent to other malformations.<sup>98</sup>

In 55 necropsy patients more than 14 years of age, isolated mitral disease causing pure regurgitation was found to be non-rheumatic almost often as rheumatic<sup>99</sup> (Table XIII). The relatively high incidence of non-rheumatic etiologies in this autopsy series may be due to the higher mortality rate of non-rheumatic mitral regurgitation, particularly of ruptured chordae tendineae.

Isolated aortic valve disease is almost non-rheumatic: in a review of 139 cases of aortic valvulopathy the incidence of congenitally formed aortic valves was 72% with very low incidence of previous history of RF and absent Aschoff bodies.<sup>100</sup> More frequent causes of atherosclerotic heart disease bicuspid aortic valve, infective endocarditis and ankylosing spondylitis. In a Scandinavian study a marked decrease in cases of RHD over the period 1930-64 was accounted for by a decrease of patients with history of RF, while the group with no history remained unchanged (Fig. 12).<sup>101</sup> This suggests that patients with findings compatible with RHD but no history of RF may have non-rheumatic cause.

Both *Yersinia* and *tricuspid carditis* as mentioned earlier may cause syndromes which clinically overlap with the spectrum of rheumatic fever; manifestations could they also in some cases be responsible for chronic valvular disease. A recent 17- to 3-year follow-up of seven patients with *Yersinia* carditis showed only ECG abnormalities in one,<sup>102</sup> but larger long-term follow-up may be worthwhile.

A viral etiology has been proposed for RHD cases without history of RF and also for RF and RHD in general.<sup>103</sup> Cardiotropic viruses like Coxsackie B have been demonstrated by immunofluorescent techniques in the myocardium of patients from routine autopsies<sup>104</sup> and in as many as 73% of atrial biopsies taken during cardiac surgery.<sup>105</sup>

Experimental infection with cardiotropic viruses in monkeys have caused valvular heart disease.<sup>106</sup> On the clinical side persistence of seemingly organic murmurs has been reported for at least 6 to 8 months after acute viral carditis in three cases.<sup>107</sup> So the possibility that some cases of chronic valvular disease in man may be caused by viruses must be considered. That viral infections cause the garden variety of rheumatic fever however, is unlikely since penicillin prevents rheumatic fever and is ineffective against viruses—unless one postulated for viral agents a necessary but not sufficient co factor role.

The rheumatic etiology of MS has also been questioned in some cases of *Lutembacher Syndrome* deformities of the mitral valve were found without evidence of previous endocarditis or thrombosis suggesting that the mitral valve pathology is due to fibrotic reaction to altered flow patterns.<sup>108</sup> In another series of five well studied cases however four had a history of rheumatic fever.<sup>109</sup>

**Mitral valve prolapse and RHD** Mitral valve prolapse (MVP) is a syndrome characterized by "non ejection systolic clicks and mitral systolic murmurs accompanied by anginal symptoms cardiac arrhythmias and ECG abnormal findings."<sup>110, 111</sup> It is of interest in connection with RHD because (1) its physical signs overlap in part with those of rheumatic mitral valve disease and may therefore be misdiagnosed or such and also (2) because RF may be one of its causes. Its study is not made any easier by the wild variations of its reported prevalence which has varied tenfold even in the same laboratory according to the "index of suspicion and the related carefulness of the physical examination.

The overlap between rheumatic mitral regurgitation and mitral valve prolapse is exemplified by a series of 130 cases of MVP rheumatic etiology was considered probable in eight and definite in 13 on the basis of history.<sup>112</sup> (Fig 13) In another clinic 18.5% of 185 cases of rheumatic carditis characterized initially by blowing pansystolic

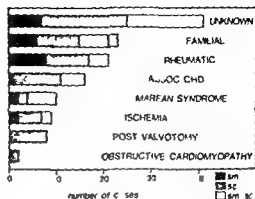


Fig 13 Probable etiology of mitral valve disease in 130 patients with late systolic murmurs (sm) non-ejection systolic clicks (sc) or both From Pocock, W. A. and Barlow J. B. Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome. *Am J Med.* 51:731 1971. Reproduced by permission.

murmurs developed late or mid late systolic murmurs between one month and 9 years after the attack,<sup>113</sup> and of 12 patients with previous rheumatic fever and late systolic murmur ten were shown to have mitral valve prolapse by echocardiography.

In Soweto South Africa the prevalence of non ejection systolic clicks seemed to parallel that of RHD. This led to the hypothesis that MVP might represent early RHD.<sup>114</sup> However a follow up study of children with MVP showed neither rheumatic attacks nor clinical deterioration on no prophylaxis. Obviously the relation of RHD and MVP remains an intriguing one for investigation.

We have certainly come a long way from 1924 when Coombs could state that all acquired mitral valve disease also all unexplained cardiomegaly in children are rheumatic because no alternative theory of causation is available.<sup>115</sup> (Fig 14)

### Treatment

It is ironic that the field most important to a physician treatment is the one that can boast the least progress. To be sure surgery has provided relief for the most disabling end results of carditis but the outcomes are often imperfect the operative mortality rate not negligible and whenever prostheses are involved the postoperative risk of infective endocarditis is significant and the need for perennial anticoagulation is bothersome. Most important perhaps from a

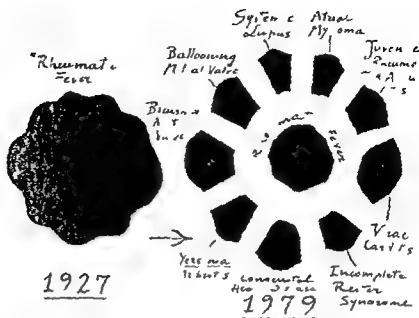


Fig 14 The whittling away of rheumatic fever. Many diseases that had not been described or were difficult to diagnose in 1927 (the particular year is arbitrary) were "lumped" into rheumatic fever (in the presence of fever) or with rheumatic heart disease (in its absence). They are now split off. What remains is a core, smaller but more homogeneous than the original lump.

Table XIV Effect of salicylate on acute rheumatic fever\*

	Treatment	
	Salicylate (N = 60)	Placebo (alkali) (N = 60)
Average duration of fever	5.7 days	10.3 days
Average duration of joint swelling	5.0 days	12.2 days
Development of carditis under observation	11.6%	6.6%
Relapses	26.6%	8.3%

\*From Finlay D W and Lucas R H. *Lancet* 2:420 (1937)

world wide standpoint cardiac surgery is often unavailable or difficult to get to or rudimentary in many parts of the world—the very parts in fact where the need is greatest.

Medical therapy still revolves around aspirin, steroids, and bed rest. As the antique study of Finlay and Lucas (Table XIV) already showed salicylates are effective on arthritis but not on carditis and may increase the percentage of relapses which we would now call rebounds. But only a few points are buttressed by controlled studies: the following therefore reflect our biases as much as our knowledge.

All patients with rheumatic fever should be examined daily for the first 2 or 3 weeks of the illness primarily to find out whether carditis develops and to start treatment should a failure appear. Discussion at the bedside concerning heart murmurs or cardiomegaly are better avoided often the patient misunderstands and worries needlessly.

All patients should be in bed for the first 3 weeks of illness because carditis if not already present may appear during this period. Strict bed rest however, should be limited to patients with arthritis of the lower limbs and to those with carditis and a large heart. The bed rest regime should then be tailored to the manifestations of the disease that are present in the particular patient. Those with polyarthritis only are usually asymptomatic by the second or third weeks of aspirin treatment. They may then be gradually ambulated while continuing on aspirin. Patients with significant murmurs but no definite cardiomegaly or heart failure (with or without polyarthritis) should be kept in bed for 1 week. The bed rest need not be strict, and in the last week may be broken by periods of supervised ambulation of a few hours per day. Patients with carditis and cardiomegaly but no congestive heart failure (with or without polyarthritis) should be kept on bed rest for 6 weeks; the first

weeks of which should be strict. Patients with arthritis and congestive heart failure (with or without polyarthritis) should be kept on strict bed rest until failure is controlled. It is wise to maintain a modified bed rest until a month after anti-inflammatory treatment is stopped (if no rebound ensues) or until 2 weeks after the spontaneous subsidence of a rebound.

In cases with arthralgia only or with mild arthritis and no carditis the patient may be given analgesics only. This is particularly wise when the diagnosis is not definite. Patients with moderate or severe arthritis but no carditis or with carditis but no cardiomegaly or failure will be treated with aspirin two thirds to three fourths grains per pound per day for the first 2 weeks and one half grain per pound per day for the following 6 weeks. Sometimes slightly larger doses may be necessary to control arthritis. Patients with carditis and cardiomegaly but no congestive heart failure (with or without polyarthritis) should be started on aspirin (see above). In patients with marked cardiomegaly however aspirin is often insufficient to control fever, discomfort and tachycardia or does so only at toxic or near toxic doses. These patients may then be switched to steroids (see below).

Patients with carditis and heart failure (with or without polyarthritis) should receive prednisone, starting with a dose of 40 to 60 mg per day to be increased if control of heart failure is not achieved. In cases of extreme acuteness and severity therapy should be started by intravenous administration of methylprednisone (Solu Medrol 10 to 40 mg) followed by oral prednisone. After 2 or 3 weeks, prednisone may be slowly withdrawn decreasing the daily dose at the rate of 5 mg every 2 or 3 days and adding aspirin at standard doses. Aspirin should be continued for 3 or 4 weeks after prednisone is stopped. Thus overlap therapy reduces the incidence of post therapeutic clinical rebounds.

The termination of anti-inflammatory treatment may be followed in all rheumatic fever patients by the reappearance within 2 or 3 weeks of laboratory abnormalities (laboratory rebounds) or of clinical abnormalities as well (clinical rebounds). All the laboratory rebounds and most of the clinical rebounds are best left untreated or should be treated symptomatically with analgesics or small doses of aspirin lest the full treatment be followed by another rebound

and the duration of the attack be lengthened. Only the most severe clinical rebounds necessitate reinstitution of the full original treatment.

Unfortunately most well controlled studies have failed to prove that treatment with steroids decreases the incidence of residual rheumatic heart disease. Nevertheless such treatment is indicated in patients with severe carditis and failure because of the distinct impression that death during the acute attack may be averted thereby.

In about 5 to 10% of all patients with rheumatic fever a persistently elevated erythrocyte sedimentation rate is observed for months after termination of therapy. This is a benign unexplained phenomenon that should not alter the medical management. However a persistently elevated C reactive protein level often heralds a protracted course with subsequent flare ups. These patients should be supervised closely. Once rheumatic fever has subsided and more than two months have gone by after stopping treatment with aspirin or steroids rheumatic fever does not reappear unless a new streptococcal infection occurs.

The heart failure of rheumatic carditis is often controlled with bed rest and steroids only. If it is not diuretics may be added first followed by digitalis if needed. Digitalis should be used with caution because its therapeutic range may be decreased in rheumatic carditis. The need for digitalis should be reevaluated at the end of the rheumatic attack and periodically thereafter. In assessing the effect of digitalis one should distinguish cardiac tachycardia which is also present during sleep (sleeping tachycardia) from emotional tachycardia which subsides during sleep.

Patients with chorea may benefit from administration of barbiturates or tranquilizers. Since chorea often occurs as an isolated manifestation or a few months after arthritis or carditis anti-inflammatory medication is not usually needed.

#### Prevention of rheumatic fever recurrences

For all its simplicity and lack of glamour, prevention of recurrences is the finest achievement of medicine in rheumatic fever. It is markedly effective in reducing and in fact practically in eliminating recurrences when benzathine penicillin is used. Moreover the success of secondary prophylaxis is way out of proportion to the



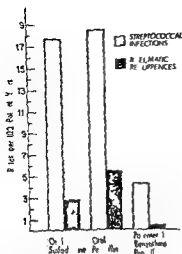


Fig 15 Streptococcal infection rates and rheumatic recurrence rates per 100 patient years in children and adolescents with previous rheumatic fever. The three prophylactic regimes were tested concurrently: sulfadiazine 1g/day orally in a single dose (675 patient years); penicillin G 0.2 million units/day orally in a single dose 1/2 hour before breakfast (545 patient years); and benzathine penicillin G 1.2 million units intramuscularly every 4 weeks (560 patient years). From Taranta A and Gordis L. The prevention of rheumatic fever: Opportunities, frustrations and challenges. *Cardiovasc Clin* 4:1 1972. Reproduced by permission.

purely numerical reduction of rheumatic fever attacks because a disproportionate number of deaths and disabilities are due to recurrences rather than to first attacks. In fact the much touted change in clinical pattern of the disease in the Western world is largely due to the reduction of recurrences.

As soon as the diagnosis of rheumatic fever is made—not sooner lest other possible diagnoses be obscured—the patient should be started on anti-streptococcal prophylaxis with an initial therapeutic (streptococcal eradicating) dose or course of antibiotics (as outlined under *Appropriate treatment* below). Thanks to this eradicating treatment one can then start continual prophylaxis with a clean slate and clearly identify new infections should they occur.

Best results are obtained with the injection of 1.2 million units of benzathine penicillin G every four weeks' (Fig 15). This is the treatment of choice; it is especially useful in high risk patients—i.e. those with rheumatic heart disease or with a recent previous attack (3 years or less) or with multiple attacks or those unlikely to take diligently a daily medication. Additional risk factors are young age (childhood and adoles-

cence) exposure to young people and crowding the home. In patients intolerant of benzathine penicillin because of pain at the site of injection, continual oral medication may be prescribed. Success of course depends on the compliance of the patient, which may be poor even when the patient seems to be cooperative.<sup>131</sup>

Sulfadiazine (0.5 g once daily in children weighing less than 60 pounds and 1 g others) and oral penicillin (200,000 to 400,000 units twice a day) are about equally effective. Patients on sulfadiazine should have a blood count after 2 weeks and also whenever they develop a rash in association with fever or throat. The drug should be stopped if the blood count falls below 4,000 and the neutrophils fall below 35 per cent. For the exceptional patient who may be sensitive to both penicillin and sulfa erythromycin may be prescribed to 250 mg twice daily.<sup>132</sup>

For maximum protection continual prophylaxis may be maintained for the lifetime of the patient. This is particularly important for patients with rheumatic heart disease. The factors mentioned earlier may serve as a guide to the physician so he may apply persuasive persuasion in accordance with the needs for protection of the particular patient.<sup>133</sup>

### Prevention of first attacks

The prevention of recurrences is useful to patients after a first attack but will not definitively eradicate the disease. The hope that some patients are forever damaged by their first attack to them the triumphs of secondary prophylaxis are no consolation. Though effective when it can be administered prior to the first attack is hampered by the huge susceptible population at risk and by the limitations of our ability to diagnose streptococcal pharyngitis, mostly because of the limitations of primary prevention that hopes are pinned on a vaccine (see below). In the meantime this can be accomplished by the diligent and intelligent application of existing knowledge.

Patients with fever, fiery red throat, exudate and tender anterior cervical nodes are more likely than others to have streptococcal pharyngitis, but even this picture may be caused by viruses. Conversely, some mild sore throats may be streptococcal.

may be followed by rheumatic fever or glomerulonephritis. Therefore, it is considered prudent\* to take a throat culture in all patients with acute pharyngitis and to treat all those with a positive culture<sup>17</sup> even though economic considerations may suggest otherwise.<sup>18,19</sup> Hoarseness, conjunctivitis, cough and simple coryza are usually not associated with streptococcal infections, therefore patients with these symptoms need not be cultured.

*The technique of taking a throat culture* is simple but often neglected. The throat culture should be taken of course before antibiotic therapy. The tongue should be depressed, the throat should be clearly visualized and well lit and the swab must be rubbed vigorously over each tonsillar area without touching the tongue or the lips. One may then send the swab to a laboratory following the laboratory's instructions or one may streak the swab directly on a blood agar plate and then incubate and read the plate.<sup>1</sup> Taking two cultures decreases the incidence of false negatives.<sup>11</sup> The cost of the throat culture which is often excessive can be reduced by using state laboratories (whenever available) or by doing the culture in one's own office. Alternatively, one may ask commercial or hospital laboratories to omit the unnecessary garnishes of identification of all bacterial species (usually the only important organisms to identify are group A beta hemolytic streptococci) and of antibiotic sensitivity (all group A beta hemolytic streptococci are sensitive to penicillin).<sup>1</sup>

When to start treatment and whether to start treatment without a throat culture depends on how sick the patient is and on how compliant he is considered to be and of course on the availability of throat cultures. Treatment may be started at once in a febrile toxic patient with exudative pharyngitis. This is particularly true for those patients who may not be expected to return for treatment. Often in emergency room practice or walk-in clinics the doctor perceives that the patient is not likely to come back and that treatment will be given either now or never—he should then treat now. On the other hand, the milder the symptoms and signs and the closer the patient-doctor relationship, the safer it is to delay treatment until an etiologic diagnosis

is made. One should remember that a few days delay in initiating treatment has been shown not to be harmful in terms of rheumatic fever prevention.<sup>1</sup>

Although many parents of patients are anxious to obtain instant treatment, experience has shown that they can be educated. In fact, in increasing numbers of middle class communities, mothers rate pediatricians on the basis of their throat culturing habits.<sup>1</sup>

If treatment is started with an oral agent before the culture results are known, the options remain open to discontinue medication the morning after if the throat culture is negative for beta hemolytic streptococci or to discontinue medication one day later if they are not of group A.

*Appropriate treatment.* Given the present state of knowledge, eradication of streptococci from the throat is the aim of treatment not only to prevent rheumatic fever but to interrupt the chain of contagion. Eradication depends upon the choice of drug and the length of time effective blood levels are maintained.

*Penicillin* is the drug on which the largest amount of favorable data have been accumulated. It can be administered by the oral route (200,000 to 250,000 units three to four times a day or even twice daily<sup>20</sup> at least 1/4 hour before or 1 hour after meals for 10 days, even though symptoms will abate earlier. Advantages of the oral route are a lower incidence of severe allergic reactions and the option to discontinue the drug if the diagnosis is not confirmed by culture or if allergy develops.

Buffered penicillin G, the least expensive preparation, seems to be just as effective in the treatment of streptococcal pharyngitis as penicillin V or phenethicillin. The chief drawback is failure to complete the prescribed course. Such failure is surprisingly common, especially in clinic or emergency room patients,<sup>21</sup> presumably because the patient, his parents and at times the doctor do not understand why one should treat a sore throat that is no longer sore. Of course the main reason for treatment is prevention of rheumatic fever and protection of contacts—not the amelioration of symptoms which is not marked at best.<sup>18</sup>

The most reliable way to guarantee adequate therapy is by a single injection of benzathine penicillin G<sup>22</sup> 0.6 million units in children weigh

\* Prudence is for the benefit of the physician as well as the patient. If a throat culture is taken, it may be lost.

ing less than 60 pounds or 1.2 million units in the others.<sup>17</sup> If a combination of procaine penicillin and benzathine penicillin is used the latter should still be given in the amounts just noted.

Penicillin allergy is a cause of genuine concern especially when dealing with adults. Care should be taken to obtain a good history and to keep epinephrine (adrenalin) at hand.

For patients with a history of penicillin allergy erythromycin should be prescribed 20 mg per pound per day in divided doses (not to exceed 1 g per day) for 10 days.

Sulfonamides which are effective in secondary prevention should not be used in primary prevention because they do not eradicate group A streptococci. Tetracyclines should not be used for the same reason.<sup>14</sup>

In some parts of the world where broad spectrum antibiotics have been used with largesse resistance to many antibiotics including erythromycin, lincomycin and chloramphenicol is spreading among streptococci. Sensitivity to penicillin persists so far.<sup>18</sup>

Family members of a patient with symptomatic streptococcal pharyngitis are at a high risk of being infected. It seems prudent therefore to culture all family contacts with recent upper respiratory symptoms and to treat those with positive cultures. Some physicians elect to treat all family contacts.

There are several good reasons to schedule follow up visits to ascertain whether the infection has cleared or is relapsing to stimulate compliance in patients on oral medication and to find out whether streptococcal sequelae have resulted. In the case of oral medication the follow up visit should be set at 2 to 10 days after the estimated end of a bactericidal concentration (14 to 16 days for 600 000 units and 21 to 28 days for 1.2 million units of benzathine penicillin).

Streptococcal relapses can be clinical and bacteriologic (sore throat with positive throat culture) or bacteriologic only (positive throat culture without sore throat).

Current recommended practice is to treat both kinds of recurrences with a second course of penicillin (preferably benzathine penicillin by injection) or erythromycin by mouth.

Rheumatic heart disease predisposes to infective endocarditis. It is advisable to administer appropriate antibiotics to patients with rheumat

ic heart disease whenever they are exposed to a procedure which causes bacteremia.<sup>19</sup>

### Anti streptococcal vaccine

For all the successes of antibiotics and other therapeutic agents infectious diseases have not been eradicated only by vaccines (or environmental sanitation). Hence the long history of attempts to develop a streptococcal vaccine and the intensive study of M proteins, the only streptococcal components that elicit protective antibodies. These efforts have long been frustrated by the failure to obtain preparations at once highly antigenic, well tolerated. Until recently even highly purified M protein preparations elicited delayed hypersensitivity reactions which seemed to be directed not to the type specific determinant, but to a common non type specific antigen associated protein or MAP.<sup>20</sup>

The classic method of preparing M protein entails hot acid extraction of the bacterial cell, its first step. By extracting the cells with physiological temperature instead of the more drastic procedure Beachey and associates<sup>21</sup> have obtained a preparation of M protein that is highly immunogenic and yet free of non type specific immunoreactivity and cross reactivity with other antigens. This important achievement paves the way for the preparation of multivalent non type streptococcal vaccines for human use.

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## Mild mitral regurgitation and the mitral prolapse fiasco

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The diagnosis, prognosis and management of severe mitral regurgitation is comparatively well understood and its exact cause is usually clear. Not surprisingly, the diagnosis of slight mitral reflux, its cause, prognosis and management creates more difficulty and confusion, though some of this appears to result from some ill-considered statements and conclusions among the vast recent literature on the subject. Indeed, physicians may be puzzled by reading of chest pain, dangerous dysrhythmias and sudden death as serious considerations in what otherwise appears to be a trivial lesion, and even more puzzled by learning of the great frequency of mitral valve prolapse on the echocardiogram, varying from 4 to 21% of the population.<sup>1-3</sup> These views are not in accord with our experience and continuing interest in this problem, which extends over more than 25 years since we wrote on the subject in 1953.<sup>2</sup> Indeed, we hold the opinion that isolated disease of the mitral valve causing mild or moderate reflux seldom causes symptoms other than those of iatrogenic anxiety, and that the prognosis for this lesion is good, excepting the small risk of infective endocarditis and the very small one of progressive regurgitation, usually as a result of chordal rupture. These divergent opinions result in uncertainties about the problem which appear to have arisen because there has been an explosion of information brought about by advances in the tools of biological research and presented

without due consideration of the cause of the mitral reflux and its natural history. Further, more there has been a tendency to take auscultatory and echocardiographic findings of reflux in isolation and to call these a syndrome—e.g. the late systolic murmur click syndrome, the prolapse syndrome, etc. It is not always appreciated that the pattern of the systolic murmur of mild reflux, whether late, late crescendo or pansystolic, is independent of the underlying pathology, which may range from a deficit in the connective tissue or an inflammatory lesion of the valve to cardiomyopathy or coronary disease.

It is interesting to recall that around the time of the first world war a mitral systolic murmur was considered to indicate serious valvular disorder, carrying a grave prognosis, reminiscent of some of the views aforementioned. This misconception was countered by McKenzie and Lewis, who stated that systolic murmurs were harmless in the absence of evidence of myocardial disease, a statement nearer the truth than many made today about mitral valve prolapse.

In 1953 the authors described 30 cases of isolated mitral reflux of varying severity, diagnosed on the basis of a pansystolic murmur or late systolic murmur with or without a systolic click, together with radiological evidence of systolic expansion and enlargement of the left atrium. The diagnosis was confirmed at necropsy in nine cases and in only one was there histological evidence of rheumatic disease. Even in the mild cases, ventricular extrasystoles and a complaint of palpitations were found to be very common, and the course was long and benign, although it was occasionally interrupted by infective endocarditis and eventually by left ventricular failure in some. It is of special interest that the systolic murmur always reached the aortic component of

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the second sound that a late systolic crescendo to the pansystolic murmur was a common finding and that in some the murmur was confined to late systole as originally described by Griffith in 1882<sup>3</sup> and by Hall in 1903<sup>6</sup> and was preceded by clicks in two patients. However, around that time systolic clicks without a murmur or with a late systolic murmur were generally attributed to an exocardial origin (Gallavardin). They were dismissed as unimportant provided that the electrocardiogram was normal and that there was no other abnormality in the cardiovascular system—another thesis which was probably nearer the mark than some currently held.

In 1961 Reid<sup>7</sup> described eight cases with systolic clicks and in three the association with a murmur which reached the aortic component of the second sound suggested that these clicks arose in the chords of the mitral valve. Barlow and associates in 1968<sup>8</sup> confirmed by ventriculography the conclusion reached by radiology and postmortem control that late systolic murmurs denoted mitral regurgitation and they showed that prolapse of the valve was the cause of the mitral regurgitation in some cases. They published these findings in a series of patients with late systolic murmurs with or without systolic clicks but unfortunately they did not differentiate the causes of the slight mitral regurgitation which varied from isolated floppy or rheumatic mitral valves to cardiomyopathy and possibly ischemic fibrosis from coronary disease. This series based entirely on the auscultatory findings resulted in the term Barlow's syndrome for any patient with a late systolic murmur with or without a click whatever the cause of the slight mitral regurgitation. Others have added to this rather confused picture. Thus Perloff and colleagues<sup>9</sup> have stated that a late systolic murmur is the auscultatory hallmark of mitral valve prolapse; it is of course the

hallmark of slight or mild mitral regurgitation which is sometimes due to prolapse. It was unfortunate that Barlow and co-workers struck a note of alarm at the frequent association of ventricular ectopics with mitral reflux despite their previous description as frequent and unimportant in this condition while also reporting three sudden and unexpected deaths although not one of these was in their own series. Two of these cases were relatives of a 17-year-old boy with ECG strongly suggesting cardiomyopathy (Ref 8 Fig 8c) with its well known predisposition to sudden death

the third case had been examined by a colleague and the only portion of the ECG available showed T inversion in Lead II. They concluded by stating that the prognosis of the syndrome is uncertain and sudden death may occur—a grave pronouncement which has come to be too readily associated with patients having a late systolic murmur with or without a click whatever the pathogenesis of the valve lesion and whether or not there is associated myocardial or conductive tissue disease. The cases of sudden death reported in the literature are few in number but are quite time and time again furthermore in every case where we have been able to find a report on an ECG, it was abnormal and often the QT interval was prolonged.<sup>10-14</sup> Even the paper by Popp and co-workers<sup>15</sup> which emphasized the frequency of repolarization abnormalities of the ECG in cases of sudden death had the misleading title 'Life threatening arrhythmias in the mitral prolapse syndrome'. Other factors associated with death or dangerous dysrhythmias have been a low serum potassium or treatment with quinidine.

### Diagnosis

There are no specific symptoms. Precordial pains are frequent in patients with mitral regurgitation and possibly more so when the cause is mitral valve prolapse. Despite many statements to the contrary it is our view that these symptoms are rarely if ever of organic origin because the pattern of pain is so variable, often submammary, a stabbing sharp or ill-defined nature persisting for minutes, hours or days and unrelated to effort although often to fatigue. Indeed the symptoms are no different from those manifested by other patients attending an outpatient clinic with cardiac anxiety and no mitral regurgitation. Furthermore we are impressed by the absence of symptoms in those patients seen for the first time who were unaware of the existence of disease. Many patients with slight mitral regurgitation are the subject of anxiety enhanced by palpitation due to extrasystoles by extensive investigations and by inadequate reassurance. There is certainly no resemblance of their pain to that of ischemic disease. We remain totally unconvinced of a significant organic basis.

The clinical diagnosis of mitral regurgitation is essentially made by auscultation and is relatively easy provided that the relationship between the

apical systolic murmur and the aortic component of the second heart sound is clearly understood. While the murmur of mitral regurgitation is invariably loudest at the apex and is often well heard into the axilla it may be mimicked in these respects by an aortic systolic murmur. The mitral murmur however reaches and embraces the second aortic sound as expected from the relation

between the left ventricular aortic and left atrial pressure pulses and it frequently has a crescendo in late systole whereas aortic systolic murmurs invariably finish before the aortic second sound. Despite some statements to the contrary in our experience exceptions to this distinction between pansystolic regurgitant murmurs and mid systolic ejection murmurs have been very rare and are usually due to failure to identify the aortic component of the second sound which may be early.<sup>3</sup>

When mitral regurgitation is slight from whatever cause the murmur is loudest in late systole but phonocardiograms often show small vibrations in early systole. When however the murmur is preceded by a click early systole may be quite clear. It seems probable that these systolic clicks even when occurring without a late murmur are often of chordal origin and it is probable (from echo evidence) that most are caused by a minimally floppy valve without regurgitation. We have ventriculographic evidence to support this in two patients investigated for coincidental coronary disease and necropsy proof in one patient who died of carcinoma of the esophagus. Difficulty arises when  $A_2$  is soft or is drowned by the systolic murmur especially when left ventricular systole is shortened by mitral regurgitation and  $P_2$  is mistaken for  $A_2$  (particularly in severe mitral regurgitation). A similar problem arises when  $A_2$  is drowned by the murmur and stops before a loud third sound, but in both cases careful auscultation by inching with the stethoscope to the base of the heart should uncover  $A_2$ . A carotid pulse recording or echocardiogram of aortic valve movement will identify aortic valve closure in difficult cases. In calcific aortic stenosis the murmurs may be maximal at the apex and  $A_2$  may be inaudible making it impossible to decide the relationship between murmur and sound the slow rising arterial pulse then usually decides the issue. Aortic systolic murmurs diminish greatly in intensity with premature beats causing diminution in stroke volume whereas mitral murmurs

change little. In mitral regurgitation due to prolapse the murmur is often louder in the standing position. In obstructive cardiomyopathy there may be a loud apical to left sternal edge murmur and its crescendo is often later than in aortic stenosis although arising in the left ventricular ejection pathway. Furthermore it may nearly reach  $A_2$  making differentiation from mitral regurgitation very difficult. A phonocardiogram will usually show the critical gap before  $A_2$ . The diagnostic difficulty in this disease may be compounded further by the presence of mitral reflux in addition to the obstructive problem but the murmur still stops before  $A_2$  and becomes louder on the patient rising from the squatting position.

In mitral reflux the arterial pulse tends to be sharp rising and jerky depending on the degree of reflux. Palpation of the apex may suggest a hyperkinetic hypervolemic ventricle depending on severity of the reflux and integrity of the muscle but in mild reflux both apical palpation and the pulse may be normal. Ventricular extrasystoles are a common feature even with mild mitral reflux. They appear to be of benign import long term follow up has shown no adverse mortality provided that the mitral regurgitation is not primarily due to coronary disease or to other serious myocardial disease.

Critical examination of the electrocardiogram is most important in patients with evidence of mild mitral regurgitation for it may give the first important clue to the cause of the disorder. A strictly normal graph apart from extrasystoles which are common enough in mild mitral prolapse is a strong pointer to primary valve disease. However a clearly abnormal electrocardiogram indicates the presence of myocardial disease which may be the cause of the mild reflux or be associated with it or which may possibly result from it. Gross abnormalities such as Q waves in inferior leads or the signs of severe myocardial hypertrophy are obvious indicators of serious myocardial disorder but the implications of lesser abnormality are often problematical. Thus the cause of isolated T wave flattening or inversion in inferior leads is mostly obscure. Such findings may be due to early muscle disease but on the other hand it is conceivable that they may be the result of prolonged abnormal tensions on the papillary muscles resulting from the dynamic disorder primarily arising in the valve.

Echocardiography provides useful information both of valve movement and of myocardial disorder but erroneous interpretation and over diagnosis are problems and normal findings do not exclude mild degrees of defect in either valve or muscle. Nevertheless correlation particularly in mitral valve prolapse with auscultation and angiography has shown the exceptional value of echocardiography in this field.

### Etiology

Mitral reflux may be due to disease which is primarily in the valve leaflets and chordae or secondary to local disease affecting the papillary muscles and adjacent myocardium or to generalized myocardial disease leading to so called functional regurgitation. Primary valve lesions may produce reflux of any degree of severity. Rheumatic fever continues to be the commonest cause of an inflammatory lesion of the valve but a prolapsing valve sometimes called a ballooning floppy or originally called a parachute valve, has superseded rheumatism as the commonest cause of isolated mitral reflux in Europe and North America. The floppy valve shows an increasing prevalence with age affecting apparently 5% of the population over the age of 50<sup>14</sup> and in a small number there is a familial incidence.<sup>15</sup> Furthermore a similar valve abnormality occurs in some generalized connective tissue disorders such as Marfan's syndrome and Ehlers Danlos disease. It has also been found in association with both types of atrial septal defect which is a special interest in that the lean asthenic habitus and high arched palate so often associated with ASD is reminiscent of the Marfan somatotype and a similar build is often found in subjects with an isolated floppy valve. These associations together with the occasional familial incidence strongly suggest a genetically determined weakness of the connective tissue which under influence of wear and tear leads to a myxomatous transformation thus leading to cusp stretching and ballooning. Other congenital lesions of the valve are relatively rare as are all forms of mitral reflux in infancy and childhood. Clefts in the mitral valve occur as part of endocardial cushion defects and fenestrations of the valve may occur in isolation. Inflammatory lesions of the valve may develop in patients who have one of the so called collagen diseases including systemic lupus, polyarteritis nodosa and rheumatoid arthritis. As in the case

of the isolated floppy valve chordal rupture may occur in any one of these conditions.

Secondary mitral regurgitation of all degrees with normal valves may arise in any of various forms of myocardial disease. Mild regurgitation is a common finding in patients who have recovered from inferior infarction—as shown by a late systolic murmur which incidentally was never observed as a result of healed anterior infarction. Mild regurgitation does appear to have a major adverse effect on prognosis in such cases. Mitral regurgitation is common in hypertrophic cardiomyopathy where the mechanism, though somewhat obscure, also probably concerns abnormal papillary muscle function.

The recognition of the etiology of regurgitation may be difficult. A history of ischemic effort (cardiac pain) immediately points to coronary artery disease with inferior ischemia or infarction as the cause. While a history of palpitations confirmed by the finding of multiple ventricular ectopics was thought to be a feature of regurgitation in general it is a probable tendency to be more frequent in patients with dilated floppy valves though not necessarily much regurgitation which can perhaps be a mechanical irritant. Abnormalities of the electrocardiogram favor myocardial disease or coronary disease but there are exceptions. It is difficult to differentiate rheumatic from prolapsing valves. With mild rheumatic regurgitation snaps and mitral diastolic murmurs even short ones are absent and a typical rheumatic thickening seen on the electrocardiogram in severe cases may not be present. Prolapse may be occasionally missed on the electrocardiogram.

### Prognosis

The apparently excellent prognosis of patients with primary mitral valve disease caused by regurgitation can only be confirmed by long follow up having regard to a variety of factors including etiology, presence or absence of rhythmia, electrocardiographic abnormalities, echocardiographic findings, and unfortunately hard information is not available. However, one series of 62 patients with normal electrocardiograms followed for nine to 22 years showed no sudden deaths despite multiple premature extrasystoles in many. Slowly increasing regurgitation was not uncommon and cul-

in one death in a patient 75 years old and there was unexpected chordal rupture in another subject necessitating valve replacement. Five patients developed infective endocarditis. In another series<sup>11</sup> all subjects had valvar prolapse but there was a wide range of dysfunction from none in patients with isolated systolic clicks to severe regurgitation in others. Not surprisingly deterioration was found to be related to the degree of regurgitation but again the outlook was generally good: sudden death occurred in one patient known to have severe mitral regurgitation and another patient who had an episode of transient ventricular fibrillation had a grossly abnormal electrocardiogram.

In our experience multiple ventricular extra systoles do not seem to have an adverse influence on the prognosis unless associated with an abnormal electrocardiogram which shows abnormalities other than or in addition to the common finding of minor T wave abnormality in inferior leads. Similar conclusions were drawn from a monitored series.<sup>12</sup> The outlook seems to be most uncertain in those rare cases where the electrocardiogram is abnormal with a prolonged QT interval with a family history of sudden death and perhaps in those cases where extrasystoles increase with exertion and fail to disappear at the height of exercise. In such cases the pathologist may find no evidence of myocardial abnormality. Whether the finding of mitral valve prolapse in such cases is a coincidence or whether it is linked in some way, possibly genetically, to a conduction abnormality resulting in electropathological disorder or whether ectopic beats become lethal under some special circumstances such as an electrolyte abnormality remains unknown.

The prognosis in patients with mild mitral regurgitation which is secondary to myocardial disease, whether ischemic or otherwise, is almost wholly determined by the nature and severity of the myocardial disorder.

#### Management of slight mitral regurgitation

Since long term prognosis is very good except for the small risk of bacterial endocarditis, the only step that should be taken apart from reassurance is to advise antibiotic prophylaxis for dental extraction. Anxiety is a dominant feature in these subjects particularly when frequent ectopics are a continual reminder of a valve lesion: the anxiety is often increased by unwise

management and any other drug therapy should be avoided if possible. Even when there are myocardial abnormalities as suggested by an abnormal ECG, suppressant drugs for ectopic beats should be avoided if possible as they are often ineffective and the apparent need for them increases anxiety. Indeed some may be dangerous particularly in the presence of a long Q-T interval. Subjects with isolated systolic clicks and no regurgitant jet do not need antibiotic prophylaxis for dental extraction. Platelet emboli causing amaurosis fugax and other transient cerebrovascular disturbances may arise from floppy valves but this is a relatively rare occurrence. Antithrombin anticoagulants are not justified.

#### Conclusions

1 Isolated mild mitral regurgitation is a common disorder recognized by finding a crescendo systolic murmur which may be confined to late systole or continue throughout systole and in all cases up to the aortic second sound.

2 The commonest cause seems to be prolapse of the valve sometimes suspected by finding a mid systolic click or clicks at the onset of the murmur and readily confirmed by characteristic echocardiographic features in nearly all cases. This condition is probably due to the interplay of genetic and wear and tear factors leading to degeneration and stretching of valve cusps and chordae. Rheumatic disease may cause isolated mitral regurgitation without prolapse but it is relatively uncommon without some stenosis as well.

3 Mild regurgitation is often secondary to myocardial disease—most commonly as a minor lesion after healed inferior infarction; it also occurs frequently in the cardiomyopathies. Dysfunction of the papillary muscles is probably the cause in most cases.

4 Symptoms from mild reflux are minimal and mostly due to anxiety—often precipitated by palpitations from extrasystoles. Precordial and submammary pain are common and are related to anxiety but in some there may be true cardiac pain when the primary lesion is myocardial disease.

5 The prognosis of mild mitral regurgitation is generally good—dynamically the lesion is tolerated remarkably well. Ultimate prognosis however depends on the cause. Furthermore a benign

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## Clinical pharmacology of the new beta-adrenergic blocking drugs Part 13 The beta-adrenoceptor blocking drugs A perspective

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The introduction of beta adrenoceptor blocking drugs to the armamentarium of clinical medicine has provided one of the major therapeutic advances of this century. The pioneers in this field hypothesized that beta adrenergic blockage would be beneficial in patients with angina pectoris; this assumption has now been proven beyond doubt. These pioneers could not have foreseen the large spectrum of therapeutic indications that are now being discovered<sup>1-10</sup> (Table I). Beta adrenoceptor blocking agents have been found to be efficacious in neuropsychiatric disorders, endocrine disorders as well as in disorders of other organ systems (Table II). There is little doubt that the list of therapeutic indications in all the subspecialty areas of medicine will continue to lengthen as a result of the fecund inventiveness of clinical investigators. At this juncture beta adrenoceptor blocking drugs have been approved by the United States Food and Drug Administration for the treatment of angina pectoris (propranolol, timolol, nadolol), hypertension (propranolol, timolol, nadolol, metoprolol), arrhythmias (propranolol), migraine prophylaxis (propranolol) and glaucoma (timolol).

Within the next five years, other beta adrenoceptor blocking agents with cardioselectivity, partial agonist effects, alpha adrenergic blocking activity and prolonged pharmacological half-lives may be approved. For the major cardiac

indications (hypertension, arrhythmias, angina pectoris), no one beta adrenoceptor blocker has been shown to be more efficacious than another.<sup>11-16</sup> However, the differing pharmacodynamic and pharmacokinetic properties of these drugs may reduce the incidence of certain adverse reactions and provide greater ease of administration. Each compound must be measured to the needs of each patient with assessment of the benefit-risk ratio. This ratio must also take into account the financial impact of a given choice of drug to the potential benefit of that drug in an individual patient.

The clinical observation that beta adrenoceptor blocking drugs are useful for so many different indications demonstrates the importance of the sympathetic nervous system in disease states and the role of the beta adrenoceptors in multiple organ systems. The molecular biology of the beta adrenoceptor itself is being explored and this may shed light on the nature of pharmacological receptors and their activity.

### The beta adrenoceptor: changing concepts

Thirty years ago Ahlquist<sup>17</sup> performed detailed studies in which he thought to characterize the receptors by which catecholamines such as epinephrine and norepinephrine exert their physiologic effects. His studies indicated that there were two major types of receptors: alpha and beta adrenoceptors. Adrenergic receptors have since been subclassified into discrete beta<sub>1</sub> and beta<sub>2</sub>,<sup>18</sup> as well as alpha<sub>1</sub> and alpha<sub>2</sub> subtypes. The recent development of radioligand labelling techniques have greatly aided the investigation of adrenergic receptors, their molecular properties and their physiologic regulation.

The older classical concept of adrenoceptors

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**Table I** Reported cardiovascular indications for beta adrenoceptor blocking drugs

- 1 Hypertension
- 2 Angina pectoris<sup>a</sup>
- 3 Arrhythmias<sup>a</sup>
- 4 Myocardial infarction<sup>a</sup>
- 5 Dissection of the aorta
- 6 Hypertrophic cardiomyopathy
- 7 Digitalis intoxication
- 8 Mitral valve prolapse
- 9 QT interval prolongation syndrome
- 10 Tetralogy of Fallot
- 11 Mitral stenosis
- 12 Cardiogenic shock
- 13 Fetal tachycardia
- 14 Bronchopulmonary emphysema
- 15 Pulmonary stenosis and atresia
- 16 Erythromyalgia
- 17 Hypertensive response with endotracheal intubation<sup>a</sup>
- 18 Hypertensive response with human coitus

as static entities in cells which simply serve to initiate the chain of events that lead to hormone action is no longer tenable. The newer theory is that the adrenergic receptors are subject to a wide variety of controlling influences. The result of these influences is to regulate dynamically the number of adrenergic receptors in tissues. These changes in tissue concentration of receptor sites are likely involved in mediating important fluctuations in tissue sensitivity to drug action.<sup>66</sup>

There are significant clinical and therapeutic implications of these new principles. An apparent increase in the number of beta adrenoceptors and thereby a supersensitivity to agonists may be induced by chronic exposure to antagonists. This phenomenon was described by Glaubiger and Lefkowitz<sup>67</sup> and may explain the propranolol withdrawal effect which occurs in patients with coronary artery disease upon sudden discontinuation of beta adrenoceptor blocking therapy.<sup>68, 69</sup> With prolonged beta adrenoceptor blocker therapy receptor occupancy by catecholamines would be diminished and the number of available receptors is increased. When the beta adrenoceptor blocker is suddenly withdrawn an increased pool of receptors would be open to endogenous catecholamines. The resultant adrenergic stimulation may precipitate angina or myocardial infarction.

The effects of thyroid hormone on adrenergic

**Table II** Reported non cardiovascular indications for beta adrenoceptor blocking drugs**Neuro psychiatric**

- 1 Migraine<sup>a</sup>
- 2 Parkinson's disease<sup>a</sup>
- 3 Essential tremor<sup>a</sup>
- 4 Anxiety<sup>a</sup>
- 5 Exam nerves<sup>a</sup>
- 6 Alcohol withdrawal (delirium tremens)<sup>a</sup>
- 7 Narcotic withdrawal
- 8 Cocaine toxicity<sup>a</sup>
- 9 LSD induced anxiety states<sup>a</sup>
- 10 Schizophrenia<sup>a</sup>
- 11 Lithium induced tremor<sup>a</sup>
- 12 Narcolepsy<sup>a</sup>

**Endocrine**

- 13 Thyrotoxicosis<sup>a, 70</sup>
- 14 Hyperparathyroidism<sup>a</sup>
- 15 Insulinoma
- 16 Unstable juvenile diabetes mellitus<sup>a</sup>
- 17 Renal osteodystrophy<sup>a</sup>

**Other**

- 18 Glaucoma<sup>a</sup>
- 19 Tetanus
- 20 Acne vulgaris
- 21 Acute porphyria<sup>a</sup>
- 22 Endotoxin shock<sup>a</sup>
- 23 Hemorrhagic shock<sup>a</sup>
- 24 Ureteral colic<sup>a</sup>
- 25 Urinary incontinence<sup>a</sup>
- 26 Phantom Limb<sup>a</sup>
- 27 Bile acid induced diarrhea
- 28 Spastic colon<sup>a</sup>
- 29 Dysfunctional labor<sup>a</sup>
- 30 Hypothermia and hypoxia
- 31 Disseminated intravascular coagulation<sup>a</sup>
- 32 Oleander Poisoning<sup>a</sup>

receptor numbers in experimental studies provide at least a partial explanation for therapeutic efficacy of beta adrenergic blockade in treatment of patients with thyrotoxicosis. The receptor binding sites have been shown increased in hyperthyroidism<sup>70</sup> and decreased in hypothyroidism.<sup>71</sup>

The number of beta adrenoceptors have been shown to increase with alcohol withdrawal which may explain the beneficial effects of propranolol for this indication.<sup>72</sup>

The concentrations of  $\beta$  adrenoceptors in the membrane of mononuclear cells significantly decreases with age.<sup>73</sup> This might explain the progressive resistance to  $\beta$  adrenoceptor blockade therapy reported with increasing age of

hypertensive population. As shown in a study of Buhler and associates<sup>13</sup> a good response to  $\beta$  adrenoceptor blocker therapy occurred in 90% of hypertensive patients in their twenties, but the percentage of responders fell progressively with increasing age.<sup>14</sup>

An apparent decrease in beta adrenoceptor sites has been associated with the development of refractoriness or desensitization to endogenous catecholamines a phenomenon caused by the prolonged exposure of these adrenoceptors to high levels of catecholamines.<sup>15, 16</sup> This desensitization phenomenon is not caused by a change in receptor formation or degradation but rather by catecholamine induced changes in the conformation of the receptor sites, thus rendering them ineffective. These changes are reversible over a period of hours.

$\beta$  adrenoceptor blocking drugs do not induce desensitization or changes in the conformation of receptors. They do however block the ability of catecholamines to desensitize.

The new information regarding adrenoceptors has led to a better understanding of the physiological and pharmacological mechanisms that regulate their function. These new concepts concerning adrenoceptor function and regulation should also increase our understanding of agonist activity in disease states.

#### The unresolved questions

In 1958 Powell and Slater<sup>17</sup> discovered dichloroisoprenaline (DCI) the first beta adrenoceptor blocker and for over 15 years beta adrenoceptor blocking drugs have been utilized in clinical medicine. The efficacy of these agents in a multitude of clinical situations has been well demonstrated. However there are many unanswered questions.

1 It is not resolved how beta adrenoceptor receptor blockers reduce elevated blood pressure. The postulated mechanisms include a reduction in cardiac output,<sup>18</sup> an inhibition of renin secretion,<sup>19, 20</sup> a reduction in plasma volume,<sup>21</sup> a central neural effect,<sup>22</sup> a reduction of peripheral vascular resistance,<sup>23, 24</sup> and a resetting of baroreceptor levels.<sup>25, 26</sup> The resolution of this question may uncover the etiological mechanisms of essential hypertension.

2. There is a disparity between the short pharmacokinetic half life of beta adrenoceptor block-

ers and the observed length of pharmacological effects.<sup>27, 28</sup> Can beta adrenoceptor blockers be administered to patients in less frequent dosing regimens? Are metabolites important?<sup>29</sup>

3 Can the beneficial effects of beta adrenoceptor blockers in experimental myocardial infarction<sup>30</sup> be extrapolated to patients with acute myocardial infarction? Does chronic beta adrenoceptor blocker therapy provide prophylaxis against myocardial infarctions?<sup>31</sup> Do the antiplatelet actions of some beta adrenoceptor drugs have clinical relevance in myocardial infarction prophylaxis?<sup>32</sup>

4 Do pharmacokinetic differences between beta adrenoceptor blockers<sup>33</sup> have clinical relevance? For example do drugs with increased lipid solubility and rapid uptake in neural tissue have specific advantages or disadvantages in therapy?

5 Do beta adrenoceptor blocking agents with alpha adrenergic blocking properties (labetalol)<sup>34, 35</sup> provide any advantage in therapy (i.e., coronary spasm)?

6 The applications of beta adrenoceptor blocking drugs in a wide range of clinical situations suggest that sympatho-neuro adrenal imbalances may be an important etiological mechanism in disease. The explanation of why beta adrenergic drugs work in such diverse clinical entities such as anxiety,<sup>36</sup> acne vulgaris,<sup>37</sup> and porphyria<sup>38</sup> may provide insights into the mechanism of disease processes. Perhaps the ancient Greek physicians were actually talking about sympatho adrenal alterations when they described the humors in balance<sup>39</sup> as a prerequisite to health.

#### Conclusion and summary

The discovery of the alpha and beta adrenoceptor and the successful attempts to block these receptors have provided one of the most important scientific advances in clinical medicine. The beta adrenoceptor blocking drugs have been shown to be efficacious for a host of cardiovascular and neuro-endocrine indications. The addition of beta blockers with varied pharmacodynamic and pharmacokinetic properties has not influenced therapeutic applications. However it has provided pharmacological alternatives when adverse reactions prohibit the use of a specific drug. It has not been resolved whether the differences in lipid solubility or plasma half life have



any clinical relevance when using these drugs

The simple concept of competitive pharmacological inhibition at beta adrenoceptor sites has had revolutionary implications in human therapeutics. Moreover, continued research efforts may further elucidate how the sympatho neuro adrenal function can influence disease states. The pioneers in adrenoceptor research have left us with an unfinished puzzle. It is our legacy, as the inventors of the puzzle to fit all the pieces together so that the answers to the many unsolved questions can be known.

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## Annotations

### Of generic medicine bottles

The safety proprietary containers for medicine are so safe that no one can open them—neither children nor adults. The struggle to open them is so great and the frustration so exasperating that patients with angina pectoris precipitate an attack by merely trying to take a vasodilator (Fig 1). And old feeble chronically ill people cannot even "comply" with their doctor's instructions for medication—they are too feeble to open their "safe" medicine bottles. So why even prescribe medicines? Patients cannot take them anyway. I prescribed an antihypertensive for an old feeble lady patient but no one could "press and turn" the cap to open the bottle. So frustrating and so futile were the attempts to open the bottle that we had to depend on diet and other measures for management instead of drugs. Maybe the pharmacist should be allowed to substitute an old fashioned generic bottle that patients can open in place of the new safe one.

With regard to aspirin one has to match an arrow shaped nodule on the cap with a bead on the mouth of the bottle when attempting to open an aspirin bottle. Once these markers are in line then with brute force the cap can be removed. But my cataract patients with diabetic neuropathy and without a sense of touch can never put these nodules together—so they must keep their fever or headache and must let their platelets stick" (Fig 1). The number of people who die of heart attacks trying to open their "safe" medicine bottles each year is probably greater than the number of children who have ever been poisoned by drugs in the entire history of America. The deaths of these children are reported, but the incidence of heart attacks caused by the "safe" medicine container is not—as far as I know. Everyone must die—so sudden death from opening a patented nongeneric medicine bottle is better than dying of cancer and cancer chemotherapy. I suppose it is much easier to "crack a safe in a bank than to open a safe bottle of aspirin. Old people just have no chance! Who thought of the patented "proprietary safe and more expensive medicine bottles—the generic boys? We are strongly advised to have the proprietary containers

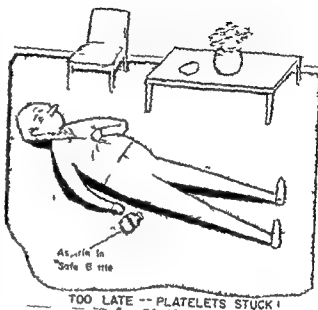


Fig 1

provided we dispense generic drugs in them. Let us save money. Let it be lawful to dispense drugs the physician considers best and allow the pharmacist to substitute a cheaper "generic" medicine container for a proprietary one so that patients, even old feeble people who still want to live happily just a few years more, can take their medicine. Perhaps we can save many lives each year and extend the life expectancy of Americans with the use of generic medicine bottles.

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### Adriamycin cardiotoxicity

The dose-limiting toxicities of anti cancer drugs are usually confined to tissues with a high mitotic rate such as bone marrow, the gastrointestinal mucosa and hair follicles. The anthracycline antibiotics daunomycin and doxorubicin (adriamycin) are exceptions to this rule. Other anti neoplastic agents have been reported to cause mild chest pain and ECG changes (5 FU) or acute mild pericarditis when used in very large single doses (cy clophosphamide). Only the anthracycline consistently induce alterations in cardiac function

which limit the safe cumulative dose of drug which can be given.

Anthracycline cardiotoxicity is an important problem for the practicing oncologist because these drugs cause regression of a variety of adult and pediatric neoplasms. Daunomycin and doxorubicin are included in the effective and probably curative regimens used to treat acute lymphatic leukemia of childhood. Doxorubicin is a principal agent in the treatment of other leukemias, Hodgkins and non Hodgkins lymphomas.

carcinogenic sarcoma breast cancer ovarian carcinoma gastric cancer and oat cell carcinoma of the lung. In addition adriamycin has been shown to have some activity in almost all adult tumor types except melanoma hypernephroma and colon cancer.

There are two distinctly different types of cardiotoxicity associated with the use of these drugs. First acute arrhythmias, non specific ST T wave changes and even clinically unapparent decreases in left ventricular ejection fractions have been observed in 5 to 100% of patients studied.<sup>1</sup> These acute effects are always transient usually asymptomatic and do not require modification of the dose or schedule of doxorubicin administration except in a rare patient with a prior history of arrhythmias. The second and more serious cardiotoxicity is the late cardiomyopathy clinically indistinguishable from idiopathic or nutritional cardiomyopathies. The congestive heart failure seen in these patients may be insidious in onset but frequently occurs abruptly as pulmonary edema precipitated by an ravenous hydration associated with cancer therapy. Heart failure usually develops within two months of the last dose of drug but instances of cardiomyopathy developing six months to almost a year later have been reported.<sup>2</sup>

The incidence (and probably the severity) of congestive heart failure is directly related to the cumulative dose of the drug. Two percent of all patients given doxorubicin develop symptoms of congestive heart failure. The incidence increases with increasing total dose to 3.5% of the patients given 400 mg/M<sup>2</sup> of those given 500 mg/M<sup>2</sup> and 15% of those who received 700 mg/M<sup>2</sup>. Most investigators have found that the incidence of cardiomyopathy is higher and the cumulative dose at onset of symptoms is lower in patients who receive mediastinal or left chest wall radiotherapy before with or after doxorubicin therapy. Concurrent therapy with cyclophosphamide or prior heart disease do not clearly increase the risk of anthracycline cardiomyopathy.

The earliest reports of doxorubicin induced heart failure suggested that it was untreatable and always fatal. Now that this is a well recognized complication of daunomycin or doxorubicin usage the drug is discontinued at the first sign of an unexplained tachycardia cough dyspnea or S<sub>3</sub> gallop and the symptoms do respond to treatment with cardiac glycosides and diuretic therapy. Recently it has been reported that children with documented pulmonary edema and cardiomegaly secondary to adriamycin may be asymptomatic without a cardiotoxic regimen and with no echocardiographic evidence of left ventricular dysfunction more than one year after the onset of symptoms.

Histologically the cardiac lesions induced by anthracyclines are not distinctly different from those associated with many other cardiomyopathies but they can be readily distinguished from lesions resulting from radiotherapy or arterial occlusion. Initially the damage is focal and scattered throughout the heart. With larger doses of adriamycin the heart is diffusely involved. The most frequent manifestations of anthracycline damage are myofibrillar lysis and cytoplasmic vacuolization. Fibrosis as typically seen after radiation damage occurs much less frequently and there is no inflammatory response.

Since no more than 30% of patients have developed overt heart failure even when quite large doses of the drug are given it seemed plausible at first that as the total dose was considerable variation in patients' susceptibility to

anthracycline cardiotoxicity. This has been studied in a number of animal models of doxorubicin cardiomyopathy. Although some species seem to be less sensitive to the drug than others all species evaluated have shown evidence of cardiac damage after doxorubicin therapy. Within each species the range of cumulative drug dose at which lesions become apparent is small, and in rabbits at least the damage is progressive. When the drug is discontinued morphologic abnormalities of the muscle have been found in monkeys after a single dose of 25 mg/kg. Cardiac biopsies of the hearts of patients given doxorubicin show typical lesions in almost all patients given 1 mg/M<sup>2</sup> or more of the drug. However it is not clearly established that the lesion is progressive in man after the drug has been stopped in one group of patients no abnormalities were seen one year after they had received 450 mg/M<sup>2</sup> a more total dose of doxorubicin. At the present time it would have to be concluded that all patients have cardiac damage when treated with daunomycin or doxorubicin and that all patients will become symptomatic from a cardiomyopathy if sufficient drug is given.

The pathophysiology of this cardiotoxicity is poorly understood. The anti tumor activity of the drug is thought to be related to its intercalation with DNA. Since other antitumor drugs with a similar mechanism of action do not cause cardiomyopathy it seems unlikely that intercalation is an adequate explanation of the unique cardiotoxicity associated with the anthracyclines. The hearts of rabbits treated with doxorubicin have abnormally high tissue levels of calcium and it has been proposed that adriamycin induced changes are due to a calcium mediated necrosis. However attempts at preventing the cardiotoxicity using chelating agents in animal models have been unsuccessful. Adriamycin has a glycosidic structure and specifically inhibits sodium potassium activated ATPase. This suggests that the doxorubicin effect might occur at the same site as digitalis toxin or that a common receptor for the anthracyclines and the cardiac glycosides might be necessary for uptake of the drugs into the heart. Currently available data suggest that strophanthidin will not block doxorubicin uptake in experimental models and there are insufficient data to justify clinical trials using pretreatment with digitalis compounds. In a recently reported study of doxorubicin cardiotoxicity in rabbits histamine and catecholamine blocking agents used together seemed to prevent the appearance of a cardiomyopathy. This suggests another possible mechanism that could explain both the acute and chronic effects of doxorubicin on the heart.

Doxorubicin also inhibits Co Q (Ubiquinone) enzymes in isolated mitochondria and the administration of Ubiquinone to rabbits or rats has been found to at least partially block some of doxorubicin's cardiotoxicity. However Ubiquinone is also a free radical scavenger. Recent data have been reported which strongly suggest that doxorubicin's cardiotoxicity and possibly even the anthracycline's tumor effect is mediated either through the production of superoxides or by activation of the anthracyclines to a free radical state. It has been shown in mice that lipid peroxidation and acute histologic changes in murine heart muscle are prevented by pretreatment with a tocopherol, another free radical scavenger. No convincing data have yet been reported to suggest that Ubiquinone or a tocopherol could be used to either decrease the incidence of heart failure

increase the cumulative doses of drug which can be safely administered to patients

Other methods used to ameliorate the cardiotoxicity of adriamycin include (1) the use of a weekly rather than a weekly interval between drug doses. The more frequent administration of smaller doses appears to decrease the incidence of heart failure but clearly does not eliminate heart damage. (2) Promising analogues of doxorubicin have been developed, some of which have decreased cardiac toxicity when used in animal systems. Several of these drugs have now entered clinical trial.<sup>14</sup>

A number of noninvasive tests and parameters of left ventricular function have been used to monitor patients receiving adriamycin therapy. These include systolic time intervals derived from phonocardiograms and ejection fractions determined from echocardiograms.<sup>15</sup> All of these studies demonstrate a deterioration of left ventricular function in groups of patients given increasingly large cumulative doses of the drug. None of these tests have proven valuable in predicting that a patient will develop a cardiomyopathy far enough in advance of symptoms to allow much adjustment of drug dosage.<sup>16</sup>

Up to one third of patients may have transient or permanent abnormalities in systolic time intervals or ejection fractions before cumulative doses of 500 mg/M have been given. Congestive heart failure in these patients is uncommon and the routine use of such studies may encourage the physician to prematurely and inappropriately discontinue chemotherapy in many patients. It has been suggested that the cumulative dose limit might be cautiously raised beyond 500 mg/M in some patients if serial studies are obtained before each dose of the drug is given. This also has not proved possible since patients with perfectly normal studies have developed pulmonary edema within 1 to 2 months of their last normal study and their last dose of adriamycin.<sup>17</sup>

Recently a study utilizing ejection fractions derived from first pass radionuclide angiography purported to show that this test was more specific than the use of phonocardiograms or echocardiograms. It is not clear why this should be so since the doxorubicin lesion is diffuse and there is no reason to expect that left ventricular wall motion will not be uniform. This approach needs confirmation with a larger group of patients in a direct comparison with echocardiography.

The most specific evaluation of cardiotoxicity is that of the Stanford group using endomyocardial biopsy. They have devised a semi quantitative scoring system. The mean score increases in patients given cumulative doses from 40 to 540 mg/M. In the Stanford studies these biopsies are performed in outpatients and the morbidity is low. The test has the advantage of providing information independent of changes in left ventricular function which are dependent upon both the doxorubicin effect and the work load placed on the heart. Because of the invasiveness of this approach it has not been used extensively in other centers. Further it is still not clear whether a low or negative score is meaningful at an early stage when lesions are focal and scattered. At present endomyocardial biopsy is the most specific way to determine anthracycline cardiotoxicity short of clinically apparent heart failure. It is probably the most useful tool available to evaluate anthracycline analogues in man.

Doxorubicin is likely to continue to be a major component of oncologic regimens until there are agents which specifically

block doxorubicin cardiotoxicity or analogues which are equally efficacious with no cardiotoxicity. At present a cumulative dose limit of 450 to 500 mg/M should be observed except in the infrequent patient in whom the threat of disease and the benefit of further doxorubicin therapy clearly outweigh the threat of heart failure. The routine use of serial noninvasive studies of left ventricular function are not of proved value in decreasing the incidence of doxorubicin induced cardiomyopathy.

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## Vascular permeability factor and nephrotic syndrome\*

The nephrotic syndrome consists of a disturbance of glomerular permeability resulting in albuminuria, hypoalbuminemia and edema. In childhood the majority of cases respond to corticosteroid therapy and have only minimal histological changes in the glomeruli evident on light microscopy. A number of clinical observations have suggested an immunopathogenesis of the steroid responsive nephrotic syndrome relapse following infection, association with atopy and response to desensitization, association with Hodgkin's disease, association with HLA-B12, response to corticosteroids and alkylating agents, and response to measles and measles vaccine. A number of these observations suggest that minimal change nephropathy is produced by a systemic abnormality of T lymphocyte function resulting in the release of a circulating

chemical mediator toxic to the glomerular basement membrane. The lack of evidence of a humoral antibody response induced by measles which modifies cell mediated immunity and the therapeutic benefits of steroids and cyclophosphamide which ablate cell mediated responses support this hypothesis.

Lymphocytes may be divided by their responses into two broad groups, thymus dependent (T) cells which are present in the delayed hypersensitivity reaction and antibody secreting (B) cells. In vivo these cell populations are interdependent. T-cells mediate the antibody response pathway, B-cells to antigen. T and B-cells act together with other cells (i.e. macrophages and polymorphs) in producing immunoregulatory effects. However the pathogenesis of a given disease depends more heavily on either T or B-cell activity.

When T lymphocytes are stimulated specifically with antigen they elaborate a variety of soluble factors termed lymphokines.

\*The author was supported by Grant from the National Kidney Research Fund of Great Britain.

times which display different biological activities. One of these the skin reactive factor has been extensively studied in guinea pigs. This factor induces a rapid increase in vascular permeability at the inter dermal site of injection. Using the Evans Blue technique Lagrue and associates demonstrated that stimulated peripheral lymphocytes from nephrotic patients produced a soluble factor that increases the vascular permeability of guinea pig skin and proteinuria on injection in the renal artery of a rat. They presented pharmacological evidence suggesting that the lymphokine activated the Kimm system.

Boulton-Jones and Simpson have recently demonstrated that lymphocytes from patients with minimal change nephropathy produce abnormal amounts of vascular permeability factor during relapse even in the absence of an *in vitro* stimulant, postulating that they have already been stimulated *in vitro*. Couser and colleagues were unable to detect differences in vascular permeability factor between nephrotic patients and controls. We have also been unsuccessful in attempting to demonstrate a lymphokine effect released by lymphocytes of nephrotic children in relapse of their disease prior to treatment with corticosteroids.

The data presented to date on this aspect of lymphocyte function in the nephrotic syndrome are intriguing but do not present a coherent picture and the suggestion that the syndrome results from a disorder to T-cell function remains speculative.

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## Cardiopulmonary bypass and postoperative neurologic dysfunction

The reported incidence of neuropsychiatric dysfunction following open heart surgery and cardiopulmonary bypass (CPB) is variable. Javid and associates reported that while 50% of patients undergoing CPB sustained a transient disorder of neurologic function, only 14% had residual cerebral deficit at the time of discharge. Branthwaite<sup>1</sup> noted a significant alteration in cerebral electrical activity during cardiopulmonary bypass in 63% of patients, but only 8% (10 of 140) had any postoperative neurologic damage. Lee and co-workers

observed neither neuropsychiatric complications nor mortality in a group of patients undergoing cardiac reparative surgery without CPB. However, patients exposed to extracorporeal circulation sustained an incidence of 23% neurologic deficit and 14% psychiatric deficit. Further, in the CPB group the mortality rate was three times higher in the subgroup of patients who had sustained neuropsychiatric deficit. Similar results were observed in our surgical intensive care unit. Patients who exhibited psychiatric dysfunction postoperative-



**Table 1 Risk factors for the development of postoperative neuropsychiatric dysfunction\***

<b>Patient</b>	
Age	
Cerebrovascular disease	
Neurologic disease	
<b>Cardiac disease—</b>	
Type	
Severity	
Duration	
<b>Operative</b>	
Hypotension (BP < 90 mm Hg)	
Blood transfusion	
Hypoxia	
Hypocapnia	
<b>Cardiopulmonary bypass</b>	
Duration	
Flow	
Pressure (BP < 50 mm Hg)	
Blood volume	
Embolus—gas, particulate matter, microemboli, fat emboli	
Hypoxia	
Hypocapnia	
Oxygenator	
Temperature	
Hematocrit	
<b>Postoperative</b>	
Hemodynamic	
Metabolic	
Environmental	

\* Reproduced from Barash, P. G. et al. Assessment of cerebral function during cardiopulmonary bypass. *Heart & Lung* 8:280, 1979.

patients were at higher risk for mortality (31%) than the control population (12%) and required three times the length of stay.

Risk factors for central nervous system (CNS) dysfunction can be related to the patient's pre-existing disease as well as to the specific perioperative experience: anesthesia, surgery, cardiopulmonary bypass, and postoperative period (Table 1). Of these variables, those related to the patient are probably the most significant. Age (> 50 years) and the presence of pre-existing neurologic or cerebrovascular disease increases the risk of postoperative deficit. Using non-invasive evaluation, Diethrich and colleagues reported that 50% of patients (mean age = 63 years) scheduled for elective open heart surgery had significant cerebrovascular abnormalities requiring further preoperative diagnostic evaluation by invasive methods. In five patients carotid endarterectomy was performed prior to or simultaneous with their cardiac surgery. The duration, severity, and type of cardiac disease are other important patient factors. Valvular heart disease is particularly at an even higher risk. CNS damage following aortic valve replacement is two times greater than that compared to open heart surgery without valve replacement.

Of the operative risk factors, hypotension, hypoxia, and hypothermia are probably the most important. Hypotension, hypoxia, and hypothermia

employed may affect postoperative neurologic function. Gerson and associates demonstrated that a membrane oxygenator resulted in improved visual motor testing when compared to a bubble oxygenator. At the onset of CPB, a number of pathophysiologic changes occur. In addition to the maintenance of non-pulsatile flow, changes in cerebral venous pressure, hemoglobin (dilutional anemia), concentration of intracerebral oxygen and carbon dioxide tensions can be observed. These are capable of causing marked alteration in the regulation of cerebrovascular activity. During CPB, maintaining adequate tissue perfusion by optimal perfusion pressure and flow must be assured. Stockard and co-workers reported that six out of seven patients who sustained prolonged hypotension during CPB had significant postoperative neurological deficits. They concluded that (1) during CPB a mean blood pressure of 50 mm Hg was critical and in elderly patients with cerebrovascular disease that a perfusion pressure of 70 mm Hg may be required; (2) risk and severity of deficits are related to the degree and duration of hypotension; (3) CNS monitoring could be prevented by the use of vasopressor agents if hypotension occurs. The duration of CPB also contributes to neurologic morbidity. Prolonged perfusion pressures (greater than 120 to 180 minutes) are associated with a two to threefold increase in neurologic deficits.

Microembolization to the brain during CPB has been previously hypothesized to be a major cause of neurologic dysfunction. Aguilar and associates found fat emboli in 78% of autopsied cases. Non-fat emboli (fibrin clots, striated muscles, platelets and fibrin aggregates) were found only when perfusion exceeded 90 minutes. With the introduction of microfilters into the CPB circuit, a marked decrease in neurologic deficit has been noted. The use of a Dacron filter reduced the incidence of cerebral non-fat emboli from 31% to 4% which was associated with a reduction in hospital mortality rate from 20% to 1%.

Monitoring of CNS function during open heart surgery is crucial. Evaluation of the patient with a thorough preoperative history and examination is mandatory. However, during the surgical procedure, the neurologic examination may be a limited value. General anesthetics, muscle relaxants, and other ancillary medications (atropine, trimethaphan, catecholamines, etc.) can obscure or camouflage signs of CNS damage. Occasionally, pupillary signs may demonstrate a focal neurologic deficit. In addition, sinus arrhythmia or bradycardia may herald the elevation of intracranial pressure. However, these are relatively nonspecific and may be related either to intrinsic cardiovascular pathology and when present, are late in the development of intracranial compression.

Direct monitoring of CNS function includes measurement of electrical activity, metabolism, blood flow, and intracranial pressure. The current "gold standard" for measurement of electrical activity is the electroencephalogram (EEG). Although EEG monitoring provides valuable data, it is not universally employed during open heart surgery and CPB. The noisy electrical environment of the operating room can obscure the recording of minute voltages. The recordings are voluminous and do not readily lend themselves to interpretation and trending. In many cases, a special technician is required to operate the electroencephalograph and to select data. Unfortunately, postoperative neurological deficits occasionally result even with a normal EEG during cardiopulmonary

nonary bypass. However persistence of the asymmetrical EEG abnormality is most commonly associated with a unilateral postoperative neurologic deficit.

As a result newer techniques have evolved to overcome these disadvantages. Power spectral analysis of the EEG has been advanced as a means to overcome the aforementioned limitations and yet capitalize on the advantages of conventional EEG monitoring. In order to simplify the evaluation of intraoperative EEG tracings, computer programs have been written to provide a compressed spectrum analysis of the EEG as recorded on line and displayed graphically with an X-Y plotter. A sudden shift in the dominant frequencies is readily visible even to the untrained observer. Stockard and co-workers have demonstrated that power spectrum analysis of EEG activity provides a readily recognizable pattern of change when cerebral perfusion is inadequate during cardiopulmonary bypass. A close correlation was observed between the appearance and persistence of power spectrum EEG changes and the occurrence of postoperative neurologic deficits.

Direct metabolic measurements of cerebral function, e.g., cerebral venous oxygen tension via the internal jugular bulb, have had very limited clinical application. However, the mixed venous oxygen tension (P<sub>VO</sub>) has been widely used as a measure of the adequacy of whole body tissue perfusion during CPB. The P<sub>VO</sub> represents the balance between oxygen delivery and utilization at the tissue level. Although normal P<sub>VO</sub> does not ensure adequate cerebral perfusion, low P<sub>VO</sub> can be indicative of poor tissue perfusion in general, including the brain.

Measurement of intracranial pressure is an important advance in the management of patients with acute CNS dysfunction. However, the patient undergoing open heart surgery is anticoagulated during CPB and thus this important neurodiagnostic technique is contraindicated.

A significant number of patients sustain some form of neuropsychiatric dysfunction following cardiopulmonary bypass. The factors that place the patient at greatest risk are advanced age, presence of cerebrovascular or neurologic disease, and the duration of cardiopulmonary bypass. At present, our routine clinical monitoring is relatively insensitive to early detection of neurologic dysfunction. The EEG or its variants seem to be the best direct monitor of cerebral function. This is analogous to monitoring hemodynamic performance by using only the electrocardiogram. Newer methods utilizing computer analysis and the EEG have great potential.

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# Applicability of correcting the QT interval for heart rate

To the Editor

Correcting the QT interval for heart rate (QTc) is a common and well established practice. It is assumed the QT interval consistently shortens as heart rate increases based on studies by Bazett,<sup>1</sup> by Fridencia,<sup>2</sup> by Simonson and associates,<sup>3</sup> and by others. Many of these studies contain experimental bias that limit evaluation of the QT interval changes, e.g. analysis of heart rate/QT variation was between individuals rather than within individuals.

The present questions arose from a clinical electrocardiographic review that was part of a study that evaluated the cardiovascular, pulmonary and neuromuscular effects of an experimental bronchodilator (clenbuterol) in 11 patients with reversible obstructive airways disease. Each subject had 48 measurements of QT interval following both adrenergic drugs or placebo. Three dosage strengths of the new bronchodilator were compared to two of a standard (terbutaline) and a placebo. QT intervals were measured and rounded to 10 msec intervals while heart rates were obtained from R-R intervals and were rounded to even beats per minute. Data were analyzed by analysis of variance and linear regression.

Dose related increases in heart rate were observed following administration of each bronchodilator and after a meal. Analysis of variance revealed residual changes in QTc following correction by the formula of Bazett. No residual changes were observed using either of the correction formulas of Simonson and colleagues. This suggests the latter formula was a better corrector of QT for heart rate than the more commonly used square root of the R-R interval formula of Bazett.

The present data were tested further by QT interval versus heart rate regression analysis which revealed an inverse relationship (Fig. 1) similar to the log-linear formula of Simonson and associates.<sup>3</sup> While the population data agree, line C there was a disparate relationship in some individuals—lines A and B. Individual B showed marked changes in the QT interval at nearly the same heart rate and individual A demonstrated an invariant QT with marked heart rate changes. The coefficient of determination ( $r^2$ ) representing the entire population demonstrates the same thing, i.e. "5% of the variation in QT is not explained by heart rate. Therefore population statistics such as those of Simonson and co-workers, as well as ours, may be inappropriate when applied to a specific ECG. While this has been recognized by Simonson and associates and by others, it is not generally appreciated.

The misapplication of statistical inference to a cardiac pharmacologic decision based on a prolonged QTc would be misleading in instances where the patient's QT varies widely at the same heart rate or is invariant as heart rate changes. Thus, rate correcting an individual's QT interval is appropriate when known rate related QT changes are present.

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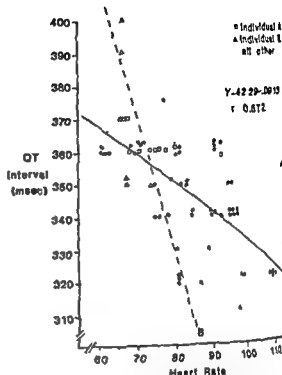


Fig. 1 A plot of all the QT intervals and heart rates. Regression coefficients for individual A (squares) and individual B (triangles) represent the extremes in variance from that of the entire group's (C). The linear regression constant, the formula  $Y = A - Bx$  are shown.

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## Improved circulation by coronary bypass?

To the Editor

I would like to say just a few words concerning Annotation by Dr Burch in a recent issue of the JOT (September 1979 Vol. 98:404) entitled "Of The quality."

Improvement of the circulation of the blood into the myocardium after bypass surgery has not been positively proved. Dr Burch and I agree that the quality of life may have been improved but its longevity is not changed.

How can it be otherwise? If we inject sap into the branches of a tree will this act improve the circulation and the color of the leaves in the fall? Surely not.

I think the same is true for the human heart. Good distal run-off for the coronary tree cannot exist when there are atheromatous plaques in the coronary arteries. I have seen ECGs unchanged after bypass surgery and I am not surprised. I thus hope nevertheless, that investigations will continue particularly as regards scanning at rest and after exercise both before and after bypass surgery.

I am reasonably certain that greater success will come from the improvement of eating habits and from the use of medications to diminish cholesterol, triglycerides, etc.

All of this is just to emphasize that I agree wholeheartedly with Dr Burch's Annotation.

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## Reduction of QRS amplitudes after cardiac dilatation

To the Editor

Lekven and associates reported recently in this JOURNAL on some very interesting ECG findings during acute dilatation of the left and right ventricles in dogs. Recording both from endocardial and epicardial electrodes they found consistently a decrease of unipolar QRS potentials with every increment in ventricular size which was induced by blood infusion under pressure. End-diastolic volume and pressure were carefully monitored during the experiments and a linear relationship between ventricular size and QRS amplitude decreases could be established.

Similar findings were reported from body surface leads by Ishikawa and co-workers in 1971. They found QRS voltage increases in the body surface ECG when cardiac size decreased and QRS voltage decreased in patients exhibiting progressive cardiac dilatation in congestive heart failure. These relatively consistent clinical observations have now been confirmed in a more direct way by the very thorough study of Lekven and associates. It has always surprised us that very little clinical use is being made of such simple observations since chest x-rays and ECGs are readily available in practically all hospitalized patients. Such QRS voltage changes are frequently interpreted erroneously as increases or decreases in left ventricular hypertrophy (LVH) when changes in cardiac size provide a much more plausible explanation.

QRS voltage decreases due to cardiac dilatation have been a puzzling phenomenon for many years and a number of hypotheses have been developed. Lekven and colleagues assume that stretching and thinning of the ventricular wall may play a role in the observed QRS decreases. Other investigators have tried to reconcile the findings with the Brody effect which is based on increases or decreases of the

intracavitary blood mass. Radial electromotive forces are expected to increase and tangential forces to decrease when the ventricular blood volume becomes larger. In the left ventricle activation has usually been assumed to be predominantly radial. This should lead to QRS increases in dilated hearts, which is contrary to actual observations. More recent studies by Roberts, Hersh, and Scher<sup>1</sup> may be quite pertinent in explaining some of the contradictory findings. They found substantially more rapid excitation parallel to the long axis of cardiac fibers than perpendicular to them. Tissue resistivity was at the same time lower parallel to the fibers by a factor of 3.2. Their results suggest a preferential spread of activation along cardiac fibers. Since the majority of the fibers have an orientation which is more or less parallel to the endocardial and epicardial surfaces one must also assume a predominant tangential spread of activation. If this is the case Brody's postulates could be reconciled with both Ishikawa's and Lekven's findings.

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## Lyle's maneuver—an overdue critique

To the Editor

Widespread acceptance of unproved diagnostic procedures is not rare in the history of medicine. It therefore does not come as a surprise that a recent editorial purports that the value of Lyle's maneuver (respiratory variation) is to differentiate benign from pathological Q waves in electrocardiographic (ECG) Lead 3. Lyle is often said to have observed that inspiration caused a Q wave in Lead 3 (Q<sub>i</sub>) to diminish or disappear among normal subjects and to persist among patients with inferior myocardial infarction (IMI). Lyle himself in presenting this data however actually stated we have not been able to gather enough cases to prove anything statistically but we believe that the cases shown illustrate certain fundamental principles.<sup>1</sup> Such anecdotal experiences are sometimes seized upon and propagated by many over time as having diagnostic value without adequate data evaluation. A survey of 166 upper Midwestern hospitals published some time ago revealed that approximately one-third of these

institutions routinely employed respiratory cycle evaluation of Lead III of the standard ECG

At least two well designed studies within the past few years have cast serious doubt upon the value of Lyle's maneuver. Shettigar and colleagues retrospectively studied 48 patients with IMI confirmed by at least two of the following findings: (1) a clinical history of acute myocardial infarction with classical ECG evolution; (2) greater than 80% narrowing of the right coronary artery on coronary angiography; and (3) significant inferior wall asynergy during contrast ventriculography. A full 20% of these patients revealed significant diminution or disappearance of Q waves in ECG Lead 3 with full inspiration!

A prospective study to evaluate Lyle's maneuver in 33 patients with IMI (classical serial ECG changes as well as positive cardiac enzyme elevations including MB Ch) and in 22 normal healthy volunteers less than 30 years of age was recently reported. Utilizing the vectorcardiogram (VCG), these authors demonstrated that approximately one half of patients with documented IMI as well as one half of normal controls with Q had an "inferior shift" in their initial 20 to 30 msec vector. An analysis of the standard ECG revealed a diminution of Q<sub>1</sub> wave depth in 61% (20 out of 33) of IMI patients and only 12% (one out of eight) of normals—results directly opposed to those predicted by Lyle! Again quoting Lyle directly concerning patients with Q and no history of myocardial infarction, she stated that "in some cases . . . we have been unable to make Q disappear or to

lower R<sub>1</sub> by inspiration so that its failure to disappear is an equivocal observation."

Certainly these recent data would suggest that Lyle's maneuver when applied to a given individual, will yield diagnostic information in the majority of cases and at times be dangerously misleading.

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## Book reviews

**Coronary Heart Disease in Young Women** Edited by M F Oliver M D London & New York 19.8 Churchill Livingstone 267 pages. Price \$3.50

This publication contains papers presented at a symposium on Coronary Heart Disease in Young Women. The presentations are interesting and extremely good. The subject of the symposium is rather unusual for symposia on arteriosclerosis. Surely the answers desired are still not available but the questions and answers clearly display the opinions of the participants and are certainly thought provoking. The reader who is actively engaged in the practice of cardiology and research and who follows the current and even the older literature will find nothing new in this publication. Nevertheless he will find the book easy to read, interesting and a good review of current concepts of the causes of arteriosclerosis and its appearance in early life as well as in young women.

**The Merck Manual—13th Edition** By Robert Berkow M D Editor and John H Talbot M D, Consulting Editor Rahway New Jersey 1977 Merck Sharp & Dohme Research Laboratories, 2165 pages

The Merck Manual is a classic among publications in medicine. Several hundred thousand are purchased each year. The Bible is the only publication which, on a regular basis, outsells this manual. The book contains a wealth of practical clinical information in general medicine. Every physician will find this to be an indispensable reference manual. It is impossible to review each subject in detail but suffice it to say that it is well indexed, clearly written and published extremely well. The first edition appeared in 1899 and the manual has continued to improve since. Each edition is better than the preceding one and of course it is always as current as any publication of this type could be. This is an excellent and valuable reference book for general medicine for students, housestaff and practicing doctors.

**Advances in Cardiology vol 24 Cardiac Rehabilitation** Edited by K Konig Waldkirch and H Denolin Basel, Switzerland 1977 S Karger AG Medical and Scientific Publisher 201 pages Price \$53.50

Cardiac rehabilitation is important in cardiac therapy. Physicians fail to realize their responsibility in this aspect of management of the cardiac patient. Cardiac rehabilitation is both overstressed as well as under considered. This book includes discussions of evaluation of cardiovascular functions

from the point of view of exercise testing, electrocardiography, therapeutic principles, psychological aspects of rehabilitation and therapeutic results and future cardiac considerations. This is a good book for internists, cardiologists and trainees. This reviewer is impressed with the lack of emphasis by physicians in clinical study of the value of the patient's ordinary daily physical and psychic responses to everyday stress rather than on hazardous and expensive treadmill exercise testing etc. in the evaluation of cardiovascular function. After all, patients walk climb stairs, mow their lawns, mend things at home, keep house etc. under daily living conditions. These are stressful activities. Why not learn how well they function at home and at work at any given time prior to and after myocardial infarction with therapy and follow up evaluation? Patients do not live on treadmills and they never will. And there is a training factor in treadmill and other exercise studies. The doctor must know his patient in order to "rehabilitate" him. Physicians can learn a great deal about patients with careful history taking. Nevertheless, this book is interesting and clearly reveals the trends in the practice of cardiology in some centers of the world and contains a great deal of interesting and useful information.

**Primary and Secondary Angina Pectoris** By Masert, Klassen, and Lesch New York 19.8 Grune & Stratton, Inc. 470 pages Price \$22.50

This book is a publication of the proceedings of an international symposium held in Pisa, Italy during June 1976. The book is divided into nine chapters, each containing several papers. The subjects discussed include experimental studies of coronary blood flow, obstructive coronary artery disease, coronary spasm ("primary" angina), prognosis, therapy and suggestions for future investigations. The emphasis on coronary spasm is evident throughout the publication. The concept of spasm of the coronary arteries in episodes of angina pectoris is certainly an old concept. However, the use of coronary angiography in patients which reveals coronary arterial constriction during "attacks" of angina has stimulated greater interest in the role of spasm. Many catheterization laboratory groups have noted the relationship of coronary artery spasm to the syndrome of angina pectoris. This publication is a good one which properly indicates the importance of not losing sight of spasms of the coronary arteries when considering the disease in patients. The contributors to the symposium were quite numerous. The book is highly recommended to all physicians.

## Books received

**Computer Techniques in Cardiology Volume 4** Edited by Lee D Cady Jr New York, 19.9 Marcel Dekker Inc. 480 pages Price \$45.00

**Dynamic Electrocardiographic Recording** By Gerald F Fletcher M D New York, 1978 Futura Publishing Company 170 pages Price \$19.50

**Biology of Brain Tumors** Edited by O D Lærum D D

Bigner and M F Rajewsky Geneva, 1978 International Union Against Cancer 209 pages. Price 15 Swiss francs

**Venenkrankheiten/Peripheral Venous Disorders** By Leo K Widmer Bern Switzerland 1978 Hans Huber Publishers 90 pages

**Stress** By Tom Cox, Baltimore 1978 University Park Press, 200 pages Price \$12.95

## Eighth Biennial Cardiology Symposium

The Johns Hopkins Medical Institutions will present an eighth biennial cardiology symposium entitled "A Review of Current Problems in Diagnosis and Therapy" to be held from June 5 through 7 1980 in Baltimore. This two and one-half day course is designed for the general internist, family physician, and the practicing cardiologist. Frequently encountered problems in the diagnosis and management of cardiovascular diseases will be emphasized. The symposium is approved for 18 Category I A.M.A. credit hours; the fee is \$150.00. For further information, contact Program Coordinator, The Johns Hopkins University, Turner Auditorium, 720 Rutland Ave., Baltimore, Md. 21205. Telephone (301) 955-5880.

## Cardiology 80

The Seventh Annual Intensive Coronary Care Symposium entitled "Cardiology 80" will be presented on June 15 through 17 1980 at the Harbour Castle Hilton Hotel, Toronto, Ontario, Canada. The symposium is sponsored by the Health Sciences Division, Humber College, Rexdale, Ontario. Fees for the symposium proper are \$80 with an additional fee of \$55 for those wishing to attend a pre-symposium one-day workshop. Twelve credit hours will be awarded by Humber College toward one course in the Certificate in Clinical Nursing; additional credits may be awarded pending approval. For further information, contact Conference & Seminar Services, Humber College, 205 Humber College Blvd., Rexdale, Ontario M9W 5L7, Canada. Telephone (416) 675-3111 ext. 539 or 540.

## Workshop on Heart Attack Prevention

The University of Minnesota Medical School is offering a workshop on the prevention of heart attacks entitled "Practical Guides to Risk Factor Reduction" to be held on June 1 through 4 1980 at Spring Hill Center, Minneapolis. For more information, contact Lori Wheatcroft, Office of Continuing Medical Education, University of Minnesota Medical School, Box 293, Mayo Memorial Bldg., 420 Delaware Street S.E., Minneapolis, Minn. 55455.

## World Congress of Pediatric Cardiology

The World Congress of Pediatric Cardiology will be held at the Wembley Conference Centre, London, on June 2 through 6 1980. Congress officers will be Dr. J. M. Edwards, Minneapolis; Dr. A. S. Nadas, Boston; Professor G. Bron, Leiden; and Professor Fergus Macartney, London. The scientific program will comprise invited lectures by outstanding international authorities; there will also be seminars and free communications. The program aims to cover all aspects of pediatric cardiology, pediatric cardiac surgery, and related disciplines. For further information, contact Secretary General, Professor Fergus Macartney, World Congress of Paediatric Cardiology, The Hospital for Sick Children, Great Ormond St., London WC1 3JH, England.

## Editorial

### Beta adrenoceptor blockade in acute myocardial infarction

R M Norris MD FRCP FRACP

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The severity of myocardial infarction depends mainly on a critical balance between oxygen supply and demand for a portion of the myocardium which may vary in size from a few grams to 40% or more of the mass of the left ventricle. This in turn is determined principally by the size of the supply territory of the coronary vessel which is narrowed or occluded and the adequacy of the collateral circulation. Experimental studies suggest that myocardial ischemia progresses irreversibly to infarction if the period of myocardial oxygen and substrate deprivation is prolonged beyond 4 to 6 hours. If coronary blood flow is restored after 3 hours however some of the ischemic tissue does not undergo necrosis.

That the anatomical lesions in the coronary circulation are not the sole determinant of infarct size has however been shown by a large body of experimental evidence from this it appears that infarct size after a standardized arterial ligation can be modified by early intervention. Of all the many interventions which are possible beta adrenoceptor blockade is perhaps the most physiologically attractive.<sup>1</sup> It has been known for many years that enhanced sympathetic activity follows myocardial infarction that levels of circulating epinephrine and norepinephrine are raised and that these hormones increase oxygen demand for the myocardium by stimulation of the cardiac beta adrenoceptors.

Although beta blocking drugs have been used successfully from the time of their introduction for reversal of the imbalance between oxygen supply and demand in angina pectoris<sup>2</sup> the history of their use in clinical myocardial infarction has been much less straightforward. This is mainly because early clinical trials ignored the short time span during which pathophysiological changes of infarction can be modified as well as the clinical pharmacology of propranolol absorption and metabolism by the liver. Moreover they did not consider the possibility that a beneficial effect of beta blockers on infarct size might happen in treated patients in the absence of a demonstrable reduction in acute mortality rate. Thus although propranolol in a dose of 40 to 80 mg daily did not reduce mortality rate in four well controlled randomized trials failure could be explained by the fact that intervention was too little and too late adequate blood levels of propranolol were almost certainly not obtained during the critical 4 to 6 hours during which infarct size might have been modified.

Use of the too little and too late dosage regime of these early trials is explainable by an exaggerated fear of left ventricular failure and collapse from beta blockers particularly if they are given intravenously. Evidence for this was mainly anecdotal<sup>3</sup> or else reported in insufficient detail. It was also to a large extent refuted by Mueller and colleagues<sup>4</sup> who showed that propranolol in a dose of 0.1 mg/Kg can be given safely intravenously to patients with uncomplicated full thickness infarcts who were studied within 24 hours of the onset of the infarct and had

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hemodynamic monitoring in a coronary care unit. Subsequent experience has confirmed their results and beta blockers have indeed been used successfully in patients with established heart failure due to congestive cardiomyopathy.

Using Mueller and associates dosage regime we have measured total creatine kinase appearance and peak levels in a randomized trial of patients seen within 12 hours of onset of an uncomplicated infarct which appeared to be transmural on electrocardiographic criteria. Although no objective clinical benefit could be demonstrated from propranolol in this group of uncomplicated patients there were no serious side effects from the drug and the enzyme levels were some 30% lower on average in patients who were treated within 4 hours of the onset than in control patients. If treatment was delayed beyond 4 hours there was no significant difference between enzyme levels in the treated and control patients. In a subsequent study of patients with a typical history of recent prolonged chest pain but no diagnostic ECG changes we were able to show that fewer completed infarcts occurred in treated patients than in controls. It thus appeared that threatened infarction in some cases could be prevented by early and adequate beta adrenoceptor blockade.

If beta blockers given early and in adequate dosage can indeed restrict infarct size it is possible that a useful effect on early mortality may be seen only in patients with potentially large infarcts which could cause shock and cardiac failure. However abolition of the inotropic adrenergic stimulus might make cardiac failure worse thus there is a potential dilemma in the use of beta blockade for the complicated patient seen early after the onset. Could treatment be given safely and with benefit for such patients? Preliminary results from our own coronary care unit suggest that intravenous propranolol given cautiously with hemodynamic monitoring and in combination with intravenous furosemide does not exacerbate cardiac failure in patients who are already in mild failure after an infarct. In a small group of such patients who had slight breathlessness radiologic evidence of interstitial pulmonary edema and a raised pulmonary wedge pressure the wedge pressure was not raised further by propranolol and clinical improvement occurred with clearing of the pulmonary edema.

tical significance can be attached to these results but they do suggest that further clinical trials using hemodynamic monitoring are indicated for patients with early cardiac failure on admission to a coronary care unit.

In addition to the above larger clinical trials are necessary using beta blockers given intravenously (if possible before admission to hospital) for patients with severe chest pain suggestive of infarction. Administration of beta blockers intravenously outside hospital would appear to be a safe procedure, provided patients were admitted immediately to a coronary care unit and provided domiciliary treatment was avoided in patients with overt heart failure hypotension, marked bradycardia or a history of asthma. Parasympathetic over activity which is as common as sympathetic over activity in the very early stages after infarction might be more pronounced after beta blockade. However excessive parasympathetic activity is less likely to be dangerous than sympathetic over activity and marked bradycardia can in any case be reversed by a small dose of atropine given intravenously. Thus increased parasympathetic activity is not an absolute contraindication to beta blockade. Large scale clinical trials of this nature will be necessary in order to determine whether restriction of infarct size by beta blocking drugs is of clinical benefit by reducing both short term and long term mortality after acute myocardial infarction.

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# IMPORTANT INFORMATION FOR AUTHORS

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# An analysis of electrocardiographic, radiographic, and vectorcardiographic findings in patients with implanted cardiac pacemakers

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Electrocardiography and lateral chest radiographs are normally used to locate the site of implanted electrodes of cardiac pacing systems.<sup>1</sup> Faults in the latter can be detected by routine bipolar lead electrocardiography but malpositioning of the implanted electrodes is more difficult to determine. The morphology of QRS complexes in a 12 lead ECG is a valuable but not an infallible guide to the site of stimulation,<sup>2</sup> while interpretation of lateral chest radiographs also has limitations. Vectorcardiograms have also been reported as being of use in the study of both the pacing system<sup>3</sup> and the intracardiac conduction system,<sup>4</sup> but little attention seems to have been paid to the pacemaker artefact stimulus and to early ventricular depolarization vectors in the detection of electrode placement errors. The present study was undertaken to determine whether the following three techniques would in combination provide a reliable indication of electrode placement errors and their site of implantation.

- 1 Pacemaker artefact vectors as determined from the three orthogonal lead ECG (and hence the vectorcardiogram)
- 2 QRS morphology from three orthogonal lead and 12 lead ECGs and
- 3 Chest radiographs

## Patients and methods

Serial 12 lead ECGs and chest radiographs (lateral and posteroanterior views) of 300 consecutive patients were recorded and studied after the implantation of permanent pacemakers. The nature of any preoperative conduction defect and site of myocardial infarction in relevant cases were also considered. Two hundred and ninety seven patients received transvenous and three had epicardial systems. The age range of patients in this group was 33 to 94 years while individual recordings were made at any time between 1 day and 8 years after the implantation. Vectorcardiograms derived from the modified axial three orthogonal lead system<sup>5</sup> were recorded in all patients who presented with abnormal x ray appearances or an abnormal ECC—i.e. not type A or B (see below)—while a sample of patients with a normal 12 lead ECG and x rays also had vectorcardiograms analyzed.

The 12 lead ECGs were classified into eight different groups as follows:

- Type A LBBB with LAD and tall R in Leads  $V_1, V_6$
- Type B LBBB with LAD and dominant S in Leads  $V_1, V_6$
- Type C LBBB with LAD  $R > 0.2$  mV in Leads  $V_1$  or  $V_6$  or  $V_1$
- Type D IVCD with extreme LAD and dominant S in Leads  $V_1, V_6$
- Type E RBBB with RAD
- Type F Probable bilateral bundle branch block with LAD
- Type G RBBB with extreme left axis deviation
- Type H Sinus rhythm

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Table 1 12 lead ECG patterns and site of implantation of pacing electrodes in 300 patients (297 endocardial, 3 epicardial)

Type	ECG patterns	Number of patients	Position of pacing electrode in lateral x ray				
			Epicardium	RV apex	RV body	RV outflow tract	Posterior
A	LBBB with LAD and tall R in V <sub>1</sub> V <sub>2</sub>	84	—	74	8	2	—
B	LBBB with LAD and dominant S in V <sub>1</sub> V <sub>2</sub>	145	—	117	17	5	—
C	LBBB with LAD and II < 0.2mV in V <sub>1</sub> V <sub>2</sub> or V <sub>3</sub>	27	—	11	12	2	2
D	LAD with RAD and dominant S in V <sub>1</sub> V <sub>2</sub>	1	—	—	—	—	1
E	RAD & RBBB	4	3	—	—	—	1
F	Probable bilateral bundle branch block with LAD	2	—	—	1	—	1
G	RBBB and extreme left axis deviation	3	—	—	—	—	3
H	Sinus rhythm	34	—	34	—	—	—
	Totals	300	3	236	38	9	14

\* Abbreviations RV = right ventricle LBBB = left bundle branch block RBBB = right bundle branch block LAD = left axis deviation  
 † RAD = right axis deviation.

The single channel electrocardiograph used to record the 12 lead ECG had a low frequency response (flat to under 50 Hz). The three lead ECGs were recorded with amplifiers having a response flat to 200 Hz and were written out on an Elema 34 ink jet writer with a superior response. While each of these frequency responses is inadequate for exact measurement of pacemaker stimulus amplitude they are sufficient to determine the polarity of the stimulus in each lead. An approximate direction of the stimulus vector can thus be inferred. This vector was classified as being directed superiorly (S) or inferiorly (I) posteriorly (P) or anteriorly (A) and to the right (R) or left (L). The mean spread of ventricular excitation up to approximately 20 msec after QRS onset was also determined from the three lead ECG and was described in similar terms. Vectorcardiographic loops were plotted on a PDP8E computer after analogue to digital conversion of the ECG signals. A typical complex was selected for display.

X rays were used to determine whether the pacing catheter was pointing anteriorly or otherwise—i.e. a line joining proximal to the distal electrode would point anteriorly in the lateral x ray of a normally implanted electrode catheter.

## Results

The 12 lead ECG patterns and radiological appearances of the implanted pacemakers in the 300 patients are summarized in Table 1. Two hundred twenty nine of these patients had a normal LBBB pattern (76.3%) type A was found in 84 (28%) and type B was found in 145 patients (48.3%). Abnormal type C LBBB (with LAD and a prominent R wave in Leads V<sub>1</sub>, V<sub>2</sub> or V<sub>3</sub>) was found in 27 patients (9%). In this group the catheter electrode pointed essentially retro sternally or towards the RV base in all but two patients in whom it was directed posteriorly (Table 1). The other ECG patterns types D to G were found in only 10 patients.

The catheter electrode system was directed retro sternally in 95% of patients although the catheter tip was in the RV body in 38 (12.7%) or in the outflow tract of the right ventricle in 9 patients (3%).

The normal pattern of the stimulus artefact was SPR in agreement with the findings of others\* although a number of patients with a normal QRS morphology and x ray appearance had an SAR pattern of stimulus artefact together with IPL or SAL initial excitation patterns the important point being a leftward ventricular depolarization. Some patients were difficult to

Table II Unusual ECG and x ray findings and the QRS vectors in 17 patients

Number of patients	Position of electrode in lateral x ray	ECG pattern	Pre-operative conduction defect	Pacing stimulus	Initial cardiac excitation	Site of implantation
1	Posterior	B	Sick sinus	SAR	SPL	RV
2	Posterior	B	MI CHB	P		
3	Posterior	B	CHB	SAR	IPL	RV
4	Posterior	B	CHB	SPR	SPL	RV
5	Posterior	B	CHB	SAR	SPL	RV
6	Posterior	C	CHB	SPR	IPL	RV
7	Posterior	C	Sick sinus	SPR	IPL	RV
8	Posterior	B	Sick sinus	SPR	SPL	RV
9	Posterior	D	2:1 AV block	SPL	SPR	RV
10	Posterior	G	L post hemiblock MI	IAR	SPR	Coronary venous system
11	Posterior	G	CHB	IAR	SPR	Coronary venous system
12	Posterior	G	CHB	SAR	SPR	Coronary venous system
13	Posterior	E	CHB	SPR	SPR	Coronary venous system
14	Posterior	F	2:1 RBBB MI	SPL	SAR	Coronary venous system
15	Anterior	C	CHB	SPL	L	Coronary venous system
16	Anterior	C	CHB	SPL	SPR	Perforation RV
17	Anterior	C	CHB	IPR	IPR	Perforation RV

RV = right ventricle MI = myocardial infarction CHB = complete heart block AV = atrioventricular  
Key to ECG patterns as in Table I Key to pacing stimulus and Cardiac Excitation as described in text

type in that the stimulus artefact was generally large and biphasic. In cases of doubt the initial component of the stimulus was chosen as indicative of the stimulus direction.

The normal pattern of early ventricular depolarization with P<sub>1</sub> stimulation was mainly SPL. This is in agreement with the findings of Zoner and colleagues<sup>1</sup> but at slight variance with the findings of Castellanos and co-workers<sup>2</sup> who referred to the initial delay of the stimulus artefact rather than to early ventricular depolarization. In their series of patients with transvenous pacing it would appear that 80% had biphasic stimulus artefact which was not the case in our series.

In all but 17 patients the ECG x ray and stimulus vector agreed on the normal or abnormal position of the pacemaker electrodes. The details of these 17 patients are presented in Table I. In 14 patients (47%) the pacing electrode system was directed posteriorly and the ECG pattern was either B C D E F or G. The initial propagation of excitation in these 14 patients is outlined in Table II which also summarizes the stimulus artefact vectors. This table also includes three other patients with an unusual combination of ECG VCG and x ray findings. Each of them had a perforated right ventricle.

## Discussion

Although the pattern of normal LBBB occurred in 229 patients (76.3%) the catheter electrode was anterior in 233 and posterior in 22, the latter group all having type B pattern stimulation of the basal portion of the right ventricle will generate an LBBB pattern with base to apex excitation while the electrical axis will point to the left and inferiorly either on account of (a) an endocardial electrode falling short of the apical position in RV or (b) an electrode bent against the septum or (c) epicardial leads implanted at the base of the RV. Since the electrode system normally lies in an anterior position—i.e., a few cm from the proximal to the distal electrode port—anteriorly the 223 out of 229 patients with type A or B ICG were regarded as having the pacemaker system in the RV apex. The six out of 229 patients with a posteriorly directed catheter system were considered as possibly having the electrodes in the coronary venous system. This point will be discussed below.

In the 27 patients with type C ECG the pacemaker electrode system was directed anteriorly in 25 and posteriorly in two. The initial QRS activation was directed to the left posteriorly and superiorly in all but three of 27 patients in whom the initial QRS vector was directed to the right posteriorly.

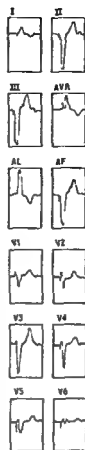
and superiorly (Fig 1) These three patients also presented with exit block and an early penetration of myocardium occurred as indicated by intermittent diaphragmatic twitching (patient No 15 Table II) presence of sanguinous effusion and clots within the pericardium (patients No 13 and 17 Table II) and resistance encountered when the catheter electrodes were dislodged at the implantation of a new epicardial electrode system

It might be postulated that the variation in the QRS pattern in the precordial leads in Types A, B and C is due to differing relationships of the left and right ventricles and the anteriorly placed stimulating electrode

Despite the widespread use of percutaneous RV pacing occurrence of an RBBB pattern during RV pacing is an infrequent finding The explanations suggested for this finding are (a) perforation or an early penetration of RV (b) retrograde conduction of the excitation wave through the conduction system of the heart\* (c) spread of impulses across the Purkinje bridge between the left and right sided conducting systems at the apex (d) high position of the electrode stimulating the mid septum which is usually thin and may therefore depolarize the LV first or (e) RV activation delay due to disease of the conducting system of the right ventricle According to Sodi-Pallares and Caldera's<sup>11</sup> concept of septal anatomy similar QRS patterns can be obtained after the stimulation of the apex of the heart at either side of the interventricular septum

The electrical stimulation of left ventricle (by an epicardial lead or an endocardial electrode misplaced into the coronary venous system [Fig 2] or by an endocardial electrode which has perforated the myocardium) provides a classical RBBB pattern<sup>10</sup> However the QRS complexes and pattern of excitation may vary with the exact site of LV stimulated The electrical axis is orientated to the right and inferior by with superior implantation If the electrode is adjacent to the apex and situated (though not orientated) anteriorly the general excitation will occur to the right posteriorly and superiorly due to the spread of excitation in the RV being dominant producing S waves from Leads V to V in the ECG (Case 9 Table II)

A more anterior position will yield an initial R wave in both Leads V and V while a slight posterior deviation produces a negative deflection in Lead V, but still with an R wave in Lead V



F

T

RS

Fig 1 The initial ventricular excitation is to the right posteriorly and superiorly in a patient with type C ECG pattern the catheter electrode was directed to the anterior

With the stimulation of the posterobasal portion of LV the activation may proceed through the septum as well as laterally and superiorly This produces LAD and the net effect in the transverse plane is a resultant anteriorly directed QRS vector giving a tall R wave in Lead V, with diminishing R waves on either side—i.e. to Leads V and V, respectively

A bipolar pacing system is an ideal model of an electrical dipole with a source and sink for electrical current which should flow directly from one electrode to the other during activation of the system Thus if the direction of the stimulus current is measured using an orthogonal lead system the approximate orientation of the electrode system can be determined electrocardiographically For example in the normal situation an electrode system will lie in the apex of the RV pointing anteriorly with the proximal electrode superiorly positioned with respect to the distal electrode The stimulus vector will then be orientated along a line from the distal to the

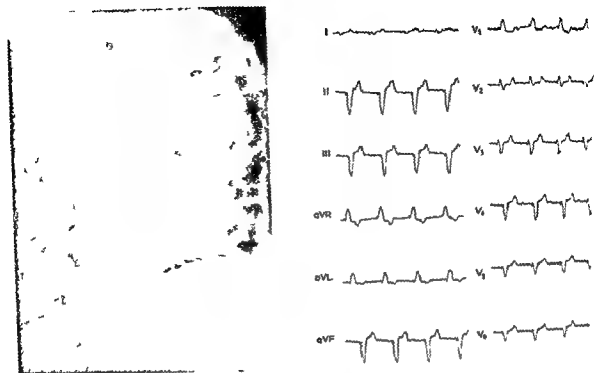


Fig 2 Lateral chest x ray the electrode system is orientated posteriorly The ECG shows LAD RBBB (Type C)

proximal electrode and normally will therefore be directed superiorly posteriorly and generally to the right side of the patient—i.e. at about 10 o'clock as seen from the front above and also as seen from the right (i.e. right sagittal view). A normal stimulus vector is therefore described as SPR. If the electrode system is directed posteriorly (Fig 2) an abnormal directed stimulus vector would be expected. This was not always found and it is suspected that at the time of operation the connection to the generator was reversed to produce an expected negative deflection of the stimulus artefact in Leads I, II and III.

With respect to early ventricular depolarization the pattern noted in the normal was SPL. With RV apical stimulation it appeared that in the typical normal the resultant ventricular depolarization was directed superiorly to the left presumably being due to the net effect of septal and LV free wall excitation in an apex base direction.

The posterior position of transvenous endocardial electrodes in a lateral chest x ray as found in 14 patients (Table II) has been considered diagnostic of malpositioned electrodes in the coronary venous system.<sup>1</sup> However interpretation of the lateral chest x ray alone can be misleading. In eight patients in the present series although the

catheter electrode was directed posteriorly (Table II) the 12 lead ECG patterns (B or C) together with the stimulus (SAR or SPR) and excitation (SPL or IPL) vectors suggest that the pacing electrode was in the RV (Fig 3 A and B). In the remaining six patients x ray ECG and vector findings were unequivocally suggestive of malpositioning of the electrode in the coronary venous system (ECG pattern D, E, F, G and initial excitation SPR) (Table II). In all but three patients with malpositioned electrodes (patients No 7, 8 and 14 Table II) intermittent failure of pacing occurred and resetting of the electrodes was necessary. After minimal displacement it was possible to advance the malpositioned electrode in the right ventricle into the main pulmonary artery at remanipulation. The malpositioned electrodes in the coronary sinus had to be passed through the tricuspid valve at the reimplantation. At each subsequent repositioning a satisfactory implantation of the electrodes into the right ventricular apex was confirmed with the help of a lateral chest x ray and vectorcardiogram.

An overzealous attempt to implant the catheter electrode into the RV apex in the frontal projection may result in bending of the catheter electrode tip against the septum or the floor of the RV. With such a malpositioned RV electrode

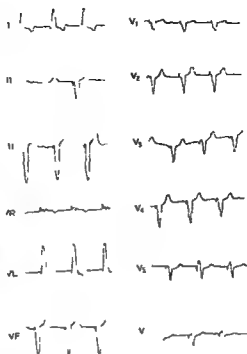
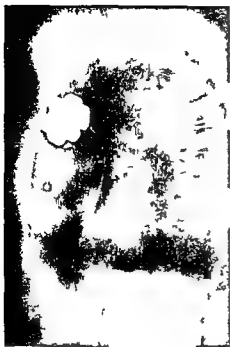


Fig 3A Lateral x ray the electrode system is orientated posteriorly The ECG shows LAD and LBBB (Type B)

the pacing may be intermittent due to the instability of the electrodes and in a lateral x ray it could point posteriorly but the excitation pattern as determined with the ECG and vectorcardiogram would indicate RV stimulation. Thus although such a malpositioned electrode in the RV may present identical to an electrode placed into the coronary venous system clinically and radiologically it can be correctly diagnosed by studying the excitation pattern with 12 lead ECG and vectorcardiogram. The findings can be summarized as in Fig 4 where a diagnostic tree is presented. From this it can be seen that the VCG findings are of value in a limited number of patients. If a strict procedure for connection of the pacemaker electrode were to be followed the posterior or anterior orientation of the electrode catheter with the help of pacemaker stimulus artefact could be inferred even in the absence of a lateral chest radiograph.

#### Conclusions

The interpretation of the morphology of the 12 lead ECG and appearances of the lateral chest radiographs are valuable but not an infallible guide to the site of implantation of the pacemaker electrodes. A simple analysis of stimulus artefact

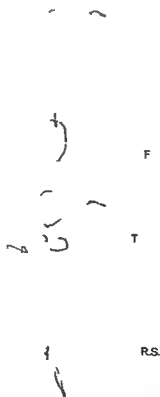


Fig 3B QRS vector of the same patient as in Fig 3A. Initial ventricular excitation is to the left, posteriorly and superiorly.



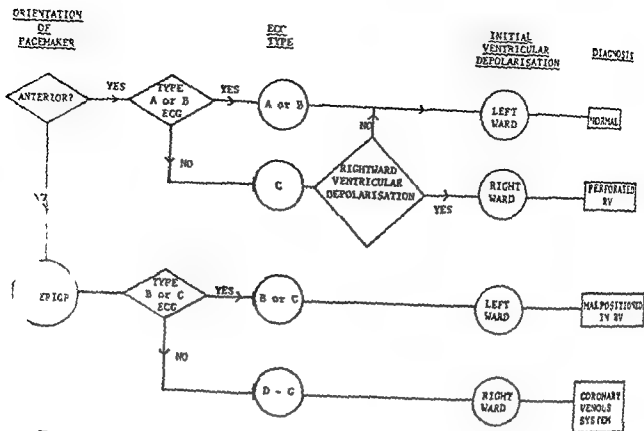


Fig 4 A diagnostic tree for orienting the pacemaker electrodes. A diamond encloses a question while a circle encloses a descriptive.

and initial ventricular vectors in combination with lateral chest radiograph, has been useful in diagnosing the electrode malposition. Errors in the post implantation position at the time of implantation

### Summary

In patients with implanted cardiac pacemakers, the radiological appearances and the configuration of the 12 lead ECG have been conventionally used both to locate the site of the electrode implantation and to diagnose electrode placement errors. These techniques have limitations and in the present study vectorcardiographic data derived from the pacemaker stimulus and the spread of ventricular depolarization has been added to improve accuracy. Three hundred patients with implanted cardiac pacemakers were studied. Unusual QRS complexes as determined from the 12 lead ECG were found in 37 (12%) and the position of the pacemaker electrodes determined from the lateral chest x ray was outside normal (RV apex) in 61 patients (20.3%). A combined interpretation of the ECG (chest x ray

and the vectorcardiogram agreed on positioning (correct or incorrect) in all but 17 patients (5.6%). Three patients had a perforated right ventricle while further study of the other 14 suggested malpositioning of the catheter electrode in the right ventricle or in the coronary venous system. An analysis of the ECG patterns, x ray appearances and vectorcardiograms is presented with respect to the diagnosis of pacemaker electrode placement errors and a logical tree for establishing the position of the pacemaker is introduced.

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# Large multiple coronary artery aneurysm in adult patients: a report on three patients and a review of the literature

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Aneurysms of the coronary arteries are uncommon. In 1929 Packard and Wechsler<sup>1</sup> found only 31 published cases in addition to that which they were reporting. In 1963, before the development of coronary angiography, Daoud and associates<sup>2</sup> published 10 personal cases and collected another 89 cases from the literature.

In spite of the widespread use of coronary angiography, coronary artery aneurysms remain an uncommon condition. Since 1963 fewer than 150 new cases have been published in the literature.

The pathogenesis of these aneurysms is still uncertain. Most coronary aneurysms are found out in patients with atherosclerosis and aneurysms discovered under these conditions are readily attributed to the atherosclerotic process. The other main etiological explanation is that they are congenital. The appearance and circumstances of the aneurysms are the main factors pointing to their etiology. In some cases, however, the appearance of the coronary aneurysms is so peculiar that they cannot immediately be attributed with certainty to one

or other of the main causes: congenital or atherosclerotic. This was the case in the three patients reported here. They were selected from about 2 000 coronary angiographies among which there were moreover ten cases with small isolated aneurysms of the coronary arteries which were the seat of advanced atherosclerosis and one case with an aneurysm of bacterial origin published previously.<sup>3</sup>

## Case reports

**Patient No. 1** S. A. 45 years old male. The patient was admitted to the hospital on June 1974 with an anteroapical myocardial infarction. There was no history of any particular illness in childhood beyond the usual ones: the patient being unable to give further details. There was no previous history of angina apart from some constricive chest pains during the days before the infarction. Certain coronary risk factors were present: moderate cigarette smoking, blood cholesterol of 2.95 g/L and mild diabetes.

In view of his relatively young age, hemodynamic and angiographic investigations were performed 2 months after the acute attack. These showed a large anteroapical aneurysm of the left ventricle considerably altering the ventricular function with an end diastolic pressure of 24 mm Hg. On coronary angiography the appearance of the coronary arteries was most unusual in that both arteries were the seat of multiple large aneurysms (Fig. 1A). The right coronary artery was distorted throughout its course by a number

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\*This survey was independently made of the two cases published by Balazs et al.



Fig 1 Case No 1 A right coronary artery in the left anterior oblique projection B Left coronary artery in the right anterior oblique projection

of large aneurysms of about 1.5 cm in diameter and several centimeters in length and the aneurysmal areas were separated by short segments of constriction the degree of which was difficult to evaluate. The distortions were such that the appearance in the left anterior oblique position was reminiscent of the colon outlined by barium. There was also a considerable dilatation with at least two aneurysmal sacs of which one was nearly 2 cm in diameter of what is seemingly a conus artery but could possibly be a circumflex artery arising from the right coronary. The left coronary artery (Fig 1B) was also the seat of a number of aneurysms mainly on the left anterior descending artery and on the diagonal branch with an aneurysmal sac of more than 2 cm in diameter at the origin of this vessel.

There was no possibility of surgery on such a coronary tree, and the patient was treated with oral anticoagulants (acenocoumarin) clofibrate and digoxin. Three years later his condition was satisfactory without evidence of cardiac failure or thoracic pain.

**Patient No 2 P B** 43 years old male. The patient was admitted to the hospital on June 6 1977 with a posterior myocardial infarction without previous chest pain apart from angina with spontaneous pains which disappeared after a few days without any special treatment when he was aged 38. The course of the infarction was satisfac-

tory. In his previous history there was a tonsillectomy at the age of 36 for frequent sore throats but this patient had no history of any particular illnesses in childhood other than the common ones no further details were obtained. As regards the coronary risk factors there was only a moderately raised blood cholesterol (280 g/L) and a little overweight.

In view of his relatively young age hemodynamic and angiographic investigations were performed 4 months after the infarction. The left ventricle was slightly dilated with moderate impairment of contractility. The end diastolic pressure was 18 mm Hg. The appearance of the coronary system was quite unusual because of the presence of several large aneurysms. The main trunk of the left coronary artery the origin of the left anterior descending artery and the circumflex artery were considerably but irregularly dilated attaining over all a caliber of more than 1 cm (Fig 2A). The first part of the circumflex artery in particular showed a fusiform dilatation which reached 1.5 cm in diameter before the vessel divided into two branches one of which was the site of two other fusiform aneurysms of 0.8 to 0.9 cm in diameter. No significant overall narrowing was seen in the left coronary tree. The right coronary artery (Fig 2B) was also the site of large aneurysms 2 to 3 cm in length especially on the right border of the heart with a diameter



Fig 2 Case No 2 A Left coronary artery in the right anterior oblique projection B Right coronary artery in the left anterior oblique projection

reaching 10 to 12 mm. Between the two aneurysms and beyond the second there was an area of narrowing which seemed to reduce the lumen of the artery considerably.

After 18 months follow up the patient had no chest pain and his activities were normal. His only treatment has been with oral anticoagulants (acenocoumarin).

**Patient No 3 J M R** 31 years old male. The patient was admitted to the hospital on November 21, 1978 for coronary angiography on account of angina pectoris. The first attack of angina was in February 1978 with pain lasting for 3 hours without definite ECG changes but with a moderate rise in CPK enzymes. Since then he had had angina of effort and an exercise tolerance test in July 1978 was positive. There was a report of high blood cholesterol (440 g/L) in 1975 and when seen following treatment with clofibrate it was 325 g/L and the triglycerides were 0.70 g/L. There was a family history of hypercholesterolemia which was also present in his mother and two sisters. There was no other special previous medical history except for the usual childhood illnesses. Clinical examination was normal as was the chest x-ray.

During hemodynamic study in the pressures were normal and the left index was 2.66 L/min/M<sup>2</sup>. Ventricular ejection was moderate

ly poor contractility with an ejection fraction of 48%. During opacification of the coronary arteries the observer was at first struck by the very peculiar appearance of the coronary network which was the seat of large aneurysms in the three main arteries. There was an aneurysm 3 cm in length and 2 cm in diameter occupying the first part of the left anterior descending artery but beyond this the artery appeared normal (Fig 3A). In the right coronary artery (Fig 3B) there were several large successive aneurysms separated by segments of artery of normal caliber and the posterior interventricular and left retroventricular arteries appeared normal. No aneurysmal dilations on the collateral branches of the aorta were apparent on thoraco abdominal aortography.

The question of a saphenous bypass graft on the left anterior descending and right coronary arteries beyond the aneurysm was discussed but as the patient was asymptomatic this was finally rejected and the patient was treated with oral anticoagulants (acenocoumarin) and clofibrate.

#### Comments

Coronary aneurysms can vary in the number of lesions, single or multiple, and all shapes and sizes can be found. They can vary from a small solitary aneurysm a few millimeters in diameter on a normal coronary tree or on altered coronary



Fig 3 Case No 11 A Left coronary artery in the left transverse projection B Right coronary artery in the left anterior oblique projection

arteries up to very large multiple aneurysms involving several branches of the coronary system. The aneurysms may be sacular or fusiform in appearance. The caliber of fusiform aneurysms may or may not be very large in which case unless they are separated by sections of artery with a normal or restricted caliber their boundaries can be difficult to determine with diffuse dilatation of the arteries which have been termed 'megadolichoid coronary arteries' or coronary ectasia.

In the survey of the subject by Daoud and associates in 1963 all the ten personal cases reported were considered atherosclerotic. There was only one case of multiple aneurysms involving both coronary arteries and there were only 11 such cases among the 89 collected by the authors from the literature. Since Daoud's review a total of 140 cases have been described in the English and French literature generally seen during life by means of coronary angiography. The number of cases discovered in relation to the total number of coronary angiograms performed was 92 in 9 105 investigations.

Four main causes of coronary aneurysms can be recognized from their clinical context and the appearance of the lesions. Congenital aneurysms are generally large and situated on one coronary artery, generally the right coronary, and are most commonly found in young subjects. Atheroscle-

rotic aneurysms are usually small in size and either localized or consisting of dilatations variable in extent with a relatively small diameter equal to or under 1 cm, associated with stenotic lesions of the usual atherosclerotic type in the remainder of the coronary risk factors. On the whole they are very uncommon in relation to the high frequency of atherosclerotic coronary artery disease. Aneurysms of bacterial origin are exceptional. They are small, solitary and can only be recognized when there is a clear history of septicemia and when the remainder of the coronary system is normal. Finally, coronary aneurysms may have an inflammatory basis but this category is usually seen in small children in association with two principal conditions: periarthritis nodosa and a special condition which was first described in Japan—the mucocutaneous lymph node syndrome. This condition, which was initially described by Kawasaki and associates in Japanese in 1967 and in English in 1974, seems to be especially common in Japan where it was first described. Up to 1977 more than 10 000 cases had been reported in that country. The syndrome is characterized by fever, exanthema, enanthema and adenopathy, and is most prevalent in male children under the age of 5, subsiding after about a fortnight. Death occurs in 1% or 2% of cases from myocardial infarction due to thrombosis of an inflamed artery or coronary aneurysm. In a

study of 20 cases in children aged 4 to 11 coronary angiography was performed some weeks or months after the illness. Coronary aneurysms five of which were multiple were found in seven cases (35%) and nonaneurysmal abnormalities were discovered in another five cases.<sup>8</sup> A later study showed the same proportion of coronary aneurysms.<sup>9</sup> This recently described illness is thus associated in more than a third of cases with coronary lesions distinguished by the number and size of the aneurysms which involve the whole coronary tree and which may sometimes regress. However although this condition was first described in Japan and seems to be unduly frequent in that country it has also been reported in other countries for example in the United States, Canada, Greece, Great Britain and France.<sup>3, 10, 11</sup> It is not therefore a specifically Japanese illness. With this syndrome could be considered periarthritis nodosa<sup>2</sup> and other panarteritis which in children may frequently cause coronary aneurysms of the same type i.e. large and multiple and involving several coronary arteries,<sup>1</sup> the histology of which is very similar to that of the mucocutaneous lymph node syndrome<sup>4</sup> and which is also capable of regressing.

Most coronary aneurysms in the literature except in the Japanese publications have been thought to be either congenital or atherosclerotic. In the patients described by Dawson and Ellison<sup>12</sup> by Ghahramani and associates<sup>13</sup> by Kaufmann and colleagues<sup>14</sup> by Mattern and collaborators<sup>15</sup> by Seabra Gomes and associates<sup>16</sup> by Wilson and co workers<sup>17</sup> as well as in 15 of the 89 cases analyzed by Daoud and associates<sup>2</sup> a congenital origin was proposed. In fact although this etiology may be the most probable in a large number of these cases quite often there is no supporting proof. Atherosclerosis is more usually proposed as the etiological factor. This was true in Daoud and colleagues' 10 patients and in 47 of the 89 patients reported by them as well as in those recorded by Anabtawi and de Leon<sup>11</sup> by Batzenschlager and colleagues<sup>18</sup> by Befeler and co workers<sup>19</sup> by Berkoff and Rowe<sup>20</sup> by Bertelsen and Lindahl<sup>1</sup> by Cherner and collaborators<sup>21</sup> by Falsetti and Carroll<sup>22</sup> by Gav and colleagues<sup>23</sup> by Kalke and Edwards<sup>24</sup> by Markus and associates<sup>25</sup> by Swanton and co workers<sup>26</sup> and by Wilson and colleagues.<sup>4</sup> Most of these aneurysms were probably really atherosclerotic mainly because most of them were seen in patients over 30 years of age.

They were not very large and they were associated with obviously atherosclerotic lesions in the remainder of the coronary system. In some patients however the atherosclerotic etiology was not obvious especially in those seen in patients aged 40 or below.

The other causes of aneurysm are much less common and those of bacterial origin are exceptional.<sup>27, 28</sup> Apart from the special situation of the mucocutaneous lymph node syndrome only a few isolated coronary aneurysms of inflammatory origin have been published. In the report by Roberts and Fetterman<sup>29</sup> the coronary arteries were involved in 18 out of 20 cases of childhood periarthritis nodosa 11 of whom had coronary aneurysms. Other cases of coronary aneurysms associated with childhood periarthritis nodosa have been reported by Bertelsen and Lindahl<sup>1</sup> by Glanz and co workers<sup>30</sup> and by Tan<sup>31</sup> and Segal.<sup>32</sup> Periarthritis nodosa is uncommon in childhood but the coronary arteries are frequently affected in this disease although this is exceptional in adults in whom the disease is more frequent. In addition isolated cases of coronary aneurysm in children have been reported by Bocquet and associates<sup>33</sup> and by Dailly and co workers<sup>34</sup> under the heading of diffuse aneuritis of undetermined etiology. In retrospect the latter case could have been due to the mucocutaneous lymph node syndrome a condition which was unknown at that time. Lastly considering those of inflammatory origin there is one case published of multiple coronary aneurysms in an adult suffering from scleroderma.<sup>35</sup> In addition to these etiological factors which on the whole occur in conditions which are fairly characteristic there are a number of cases in which the etiology remains completely unknown and the authors refrain from ascribing any cause to the aneurysms.<sup>36</sup> This includes a recent series of 47 cases<sup>37</sup> where the term ectasia rather than aneurysm was used as the lesions were characterized by diffuse dilatations.<sup>38</sup>

In the publications on this subject during the past 10 years the part played by the mucocutaneous lymph node syndrome described by Japanese authors requires emphasis. The etiology of this syndrome remains unknown but it appears to be a disease which has a very high incidence of coronary aneurysms. An extensive experience of this unusual condition led Kitamura and associates<sup>39</sup> to suggest that before a coronary aneurysm is labelled atherosclerotic or congenital one

should consider the possibility of this syndrome occurring in childhood and passing unnoticed.<sup>1</sup> On rereading the cases recorded in the literature it is noticeable that in many of these cases there are no precise facts or even any discussions on whether the aneurysms might be congenital or atherosclerotic in origin.

In the three cases reported here the coronary lesions were probably not congenital and the aneurysms by their appearance size and the fact that they involved both coronary arteries can be clearly distinguished from those recorded in most of the publications on coronary aneurysms which were considered often on flimsy evidence as atherosclerotic or congenital in origin. Bearing in mind the frequency of atherosclerotic coronary heart disease and the fairly standard characteristics of the lesions in this disease it is difficult to imagine how the aneurysms seen in these three patients could have been atherosclerotic. Angiographically the lesions were highly exceptional in the size multiplicity and distribution of the aneurysms which chiefly affected the first parts of the main coronary arteries and did not show any of the usual features of coronary atherosclerosis even on the segments of arteries which were free from aneurysms—i.e. the irregular stenotic lesions which are characteristic of atherosclerosis. One is also struck by the fact that these three cases concerned relatively young (42 and 45 years old) or definitely young (31 years old) men among the French population for atherosclerotic coronary artery disease and that no special risk factors were present in the first two cases. In the third case there was an established familial hypercholesterolemia with a blood cholesterol of 430 g/L and some small tendinous xanthomas but even so it does not seem that one can incriminate atherosclerosis as the cause of the extensive aneurysmal lesions found in the coronary network. In fact no aneurysmal lesions have been described in familial hypercholesterolemia even in the severe forms where coronary lesions are very common but of the same type as those seen in atherosclerosis in general.

In the three cases reported here it therefore seems justifiable to postulate that the lesions might have a different origin perhaps the sequel of a mucocutaneous lymph node syndrome or a regressive childhood perianteritis nodosa. The angiographic appearances of the lesions are similar to those described in the mucocutaneous lymph node syndrome and the fact that no

previous history suggestive of these two conditions is available in these patients is insufficient to exclude this possibility.

### Summary

Three cases of large multiple coronary aneurysms situated on both right and left coronary arteries were seen in three middle aged adult patients. These patients were hospitalized for myocardial infarction in two cases and for angina pectoris in the third case. On the coronary angiogram the coronary lesions were quite unusual as there were multiple voluminous aneurysms on both coronary arteries without evidence of atherosclerotic lesions of the remainder of the coronary tree. These lesions did not seem to be congenital or atherosclerotic and it was postulated that these lesions might have been the sequelae of a mucocutaneous lymph node syndrome although no previous history of this condition could be found in these three patients.

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## Evaluation of pericardial effusion with computed tomography

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Pericardial effusion has been evaluated noninvasively by the echocardiographic technique or by radioisotope methods.<sup>1</sup> However, exact information concerning the volume, distribution and nature of the pericardial effusion can not be obtained by these methods. Although computed tomography has been successfully applied in the evaluation of structural abnormalities of various organs, there have been few reports of its application to the diagnosis of heart diseases.<sup>2-4</sup>

One of the most important reasons for this appears to be the rapid motion of the heart which hinders adequate delineation of the cardiac structures by conventional computed tomographic systems. Although ECG gated methods have been developed,<sup>5</sup> our experience does not indicate that the resolution is satisfactory for analysis of cardiac structures.<sup>6</sup> On the other hand, pericardial effusion appears to be affected less seriously by cardiac motion than other cardiac structures, and

several reports have indicated the possibility of application of computed tomography for the diagnosis of pericardial effusion.<sup>7-10</sup> Therefore, in this report we have attempted to evaluate pericardial effusion with a third generation computed tomographic system.

### Methods

A computed tomographic three second whole body scanner\* which utilized a continuously rotating gantry and pulsed anode with X radiation collimated to form a thin fan-shaped beam was used. A complete section was performed in 3 seconds. The scale for transparency (CT number) was -1000 for air, 0 for water, and +1000 for bone. In the present study, no gated tomographic scanning to obtain stop-action images<sup>11</sup> was applied. Sustained enhancement was obtained with a rapid intravenous infusion of 200 ml of 30% meglumine iohalamate.

The methods were applied to 11 patients with pericardial effusion of various origins (Table I). Pericardial effusion was evaluated independently by conventional ultrasonocardiogram (UCG) methods by one of the authors (MH) on the same day as the tomographic evaluation. The computed tomographic findings were assessed without the knowledge of the echocardiographic

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\* Vista whole body CT scanner.



Fig 1 Computed tomographic findings in a normal man RV right ventricle LV left ventricle RA right atrium LA left atrium S interventricular septum The top of the picture is the anterior of the patient and the left is the patient's right side

findings by two of the authors (S M H T) The volume of pericardial effusion was calculated by measuring pericardial effusion areas on a tomogram and totaling the areas in each tomogram obtained by slicing the heart to a thickness of 1 centimeter Pericardial fluid was collected medically by inserting an 18 gauge polyethylene tube into the pericardial space via the subxyphoid approach in two patients (Cases 1 and 3) and drained surgically by pericardial fenestration in four patients (Cases 8 9 10 and 11) after completion of the computed tomographic and echocardiographic evaluation

## Results

Demonstrative cases with pericardial effusion studied with computed tomography are outlined below

Fig 1 shows an enhanced cardiac computed tomogram of a 28 year old man without any cardiovascular abnormalities At a level 7 cm

below the sternoclavicular angle the left atrium, right atrium left ventricle and part of the right ventricle are revealed (upper panel) The lower panel shows tomographic findings at the level of the right and left ventricles The top of the picture is the anterior of the patient and the left shows the patient's right side The atria and ventricles are in close contact with the lungs without any signs of pericardial effusion

Fig 2 was obtained from a 66 year old man (Case 1) with acute viral pericarditis (enhancement was not performed) The tomogram was obtained at a level 10 cm below the sternoclavicular junction The patient was obese and the transparent zone (F) surrounding the heart shows a CT number of -39 which is consistent with that of the subcutaneous fat The zone surrounding the area (F) which is indicated by E had a CT number of +20 which was lower than that of the heart muscle (CT number of +44) and was compatible with pericardial effusion The volume of pericardial fluid calculated by the tomographic technique was 431 ml and 280 ml of the fluid was removed from a canula inserted into the pericardial space via the subxyphoid route (the fluid had a yellowish color and a protein content of 4.5 gm/dl)

Fig 3 was obtained from a 66 year old woman with typical signs and laboratory data indicating hypothyroidism (Case 6) The electrocardiogram showed low voltage a chest x ray indicated marked enlargement of the cardiac silhouette and a moderate amount of pericardial effusion was detected by echocardiographic evaluation The tomogram shown in the upper panel of Fig 3 indicated pericardial effusion (E) which surrounded the right atrium and ventricles (enhancement was not performed)

The CT number of the pericardial effusion was +28 and that of the left ventricular chamber was +48 Thus x ray transparency of the effusion in hypothyroidism was lower than that observed in the patient with acute pericarditis The volume of the pericardial effusion estimated by tomography was 350 ml The lower panel of Fig 3 indicates computed tomographic findings of the same patient as shown in the upper panel but after treatment with a thyroid preparation for 9 months The effusion became clear

Fig 4 is from a 77 year old man with mitral regurgitation (Case 4) As shown in the upper panel there was marked cardiomegaly and appar

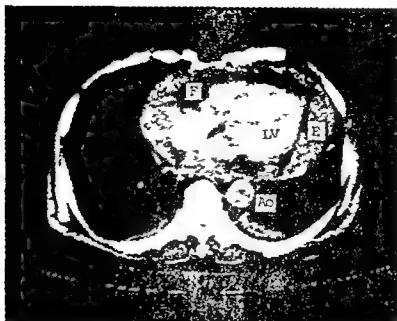


Fig 2 Computed tomographic findings of a patient with acute viral pericarditis. L: left ventricle. F: pericardial fat. E: pericardial effusion (CT number +20).

Table 1 Clinical data and computed tomographic findings in patients with pericardial effusion

Patient no	Age sex	Clinical diagnosis	Calculated volume of effusion (ml)	CT number of effusion	Detection by UCG	Collected pericardial fluid		
						Nature	Volume (ml)	Methods
1	66 M	Acute viral pericarditis	431	20	+	Yellowish	280	Medical
2	20 F	Systemic lupus erythematosus	128		+			
3	20 M	Acute viral pericarditis	371	20	+	Yellowish	130	Medical
4	77 M	Heart failure	25	13	-			
5	51 F	Renal failure	235	19	+			
6	66 F	Hypothyroidism	350	28	+			
7	60 F	Hypothyroidism	303	30	+			
8	56 F	Carcinoma (breast)	233	18	+	Yellowish	200	Surgical
9	56 F	Carcinoma (pancreas)	379	18	+	Yellowish	300	Surgical
10	58 F	Carcinoma (bronchial)	58	40	+	Bloody	500	Surgical
11	31 M	Post cardiac surgery	496	26	+	Semi bloody	400	Surgical

Not measured

ent pleural effusion with possible pericardial effusion. As shown in the lower panel, the computed tomogram at a level 7 cm below the sternoclavicular angle revealed a giant left atrium, right atrium, aorta, right ventricular outflow, and pleural effusion. A small amount of pericardial effusion (calculated tomographically as 20 ml) was delineated along the right ventricle and the lateral wall of the left atrium. The CT number of the pleural and pericardial effusion was +13. This small amount of pericardial fluid could not be detected echocardiographically.

Fig 5 is a computed cardiac tomogram of a 58-year-old woman with shock and paradoxical pulse, which were compatible with cardiac tamponade (Case 10). The fluid obtained from area E (pleural effusion) was chylous, and the fluid obtained from E<sub>1</sub> (pericardial effusion) was bloody (hemoglobin content = 103 gm/dl).

The possibility of an inadequate technique for pericardial fluid sampling could not be ruled out. On the other hand, x-ray transparency of areas F<sub>1</sub> and E was apparently different, and the CT number of area E was +40, that of area E<sub>1</sub> was

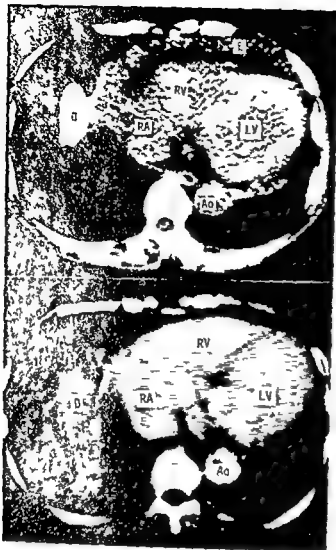


Fig 3 Computed tomographic findings of a woman with hypothyroidism RA right atrium RV right ventricle LV left ventricle Ao aorta D diaphragm E pericardial effusion (CT number +28) Upper panel is before treatment and lower panel is after treatment with thyroid preparation

+13 and that of the left ventricle was +44. Thus fluid in the pericardial and pleural cavities appeared to be of different origin. The volume of the pericardial effusion calculated tomographically was 580 ml. Pericardiectomy was performed to obtain 500 ml of bloody fluid similar to that described above and adenocarcinoma type cells were detected from the specimen. Invasion of the bronchial carcinoma into the pericardium and destruction of the thoracic duct were suspected.

Data obtained for the rest of the patients are summarized in Table I.

The volume of pericardial effusion calculated tomographically was almost compatible with that drained surgically, but it was more than the volume of pericardial fluid collected via a tube inserted into the pericardial space.



Fig 4 Computed tomographic findings of a man with mitral regurgitation during bilateral heart failure RA right atrium RV right ventricle Ao aorta LA left atrium E pleural and pericardial effusion (CT number +13)

Detection of the pericardial effusion was possible by echocardiography except in Case 4 with a small amount of localized pericardial fluid as illustrated in Fig 4.

The CT number was high in bloody pericardial effusion (+40 in Case 10, +26 in Case 11), low in renal or heart failure (+13 in Case 4, +12 in Case 5), relatively high in hypothyroidism (+29 in Case 6, +30 in Case 7), and relatively low in the rest of the patients.

## Discussion

Echocardiography<sup>1,2</sup> and radiolabeled methods<sup>3</sup> are the two most popular noninvasive methods for evaluation of pericardial effusion. However, computed tomography offers not only information on the fluid volume and its distribution but also on the gross nature of the fluid from the difference in x-ray transparency, i.e., the difference in the CT numbers. According to our experience on a limited number of patients, x-ray transparency was high in pericardial effusion due

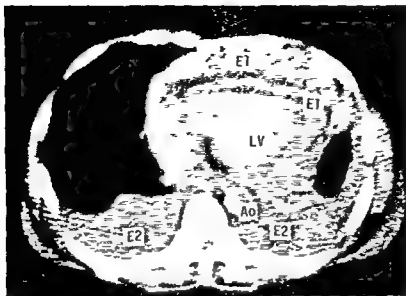


Fig 5 Computed tomographic findings of a woman with clinical signs of cardiac tamponade due to invasion of bronchial carcinoma. LV left ventricle (CT number +44) Ao aorta E<sub>1</sub> pericardial effusion (hemorrhagic CT number +40) E<sub>2</sub> pleural effusion (chylous CT number +13)

to renal or heart failure non hemorrhagic carcinomatous invasion acute viral pericarditis myx edema and hemorrhagic pericardial fluid in that order. When the pericardial effusion was whole blood logically the effusion could not be differentiated from the left ventricular cavity filled with blood. When the pericardial effusion was mixed with blood as in Cases 10 and 11 x ray transparency was higher than that of whole blood and lower than that of the exudate or transudate and the CT numbers depended on the amount of the blood contained in the pericardial fluid. Normal pericardial fluid due to myxedema was not aspirated but previous studies indicated that the fluid contained a high value of cholesterol<sup>1</sup> and this might be the reason for the relatively high CT numbers of the pericardial fluid in hypothyroidism.

The volume of pericardial fluid calculated by tomographic methods was almost consistent with the volume drained surgically but more than that aspirated by inserting a small gauge tube most probably due to the fact that complete aspiration of the fluid was not possible by the latter technique.

Evaluation of the presence and gross volume of pericardial fluid was possible echocardiographically in 10 out of 11 patients in the present study. However computed tomographic methods appear to be more sensitive concerning the minimum volume of pericardial effusion to be detected

especially when it is localized as illustrated in Fig 4.

The stop action method gated with ECG was possible with the system used in the present study<sup>4</sup> but our impression is that the quality of the tomogram is not satisfactory because of reduced data sampling numbers for every frame of the tomogram.

Without gating the effectiveness of CT scan in heart disease is limited to global diagnosis. Therefore delineation of the pericardial effusion is an adequate indication of computed tomographic applications in cardiology at present although effects of exaggerated heart movement in the pericardial fluid due to the lack of fixation of the heart by the pericardium should be taken into consideration.<sup>2</sup>

### Summary

Evaluation of pericardial effusion was attempted with computed tomography in 11 patients. The volume and distribution of pericardial fluid were assessed with satisfactory resolution and the nature of the fluid was estimated by the difference in x ray transparency (CT numbers). The volume of pericardial fluid calculated by tomographic methods ranged from 25 ml to 585 ml and agreed well with the surgically drained fluid volume. The CT numbers of the pericardial effusion due to renal or heart failure acute viral pericarditis hypothyroidism and

hemopericardium were +12 to +13 +20 +28 to +30 and +26 to +40 respectively. Therefore the volume and gross nature of the pericardial fluid could be estimated noninvasively with computed tomography.

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# Distribution and severity of left ventricular wall motion abnormalities according to age and coronary arterial pattern in 500 patients with coronary artery disease and angina pectoris\*

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The influence of age and coronary arterial pattern on left ventricular function has not been studied systematically in patients with coronary artery disease and angina pectoris. Since the adverse effects of atheromatous coronary artery disease on left ventricular performance tend to be progressive it might be expected that different distributions or severity of left ventricular wall motion abnormalities would be encountered in patients of different ages with symptomatic coronary artery disease. Furthermore specific coronary arterial patterns of Right Mixed and Left systems might also influence the distribution and severity of left ventricular wall motion abnormalities as a result of differing distributions of myo-

cardial blood flow. Therefore we undertook a meticulous review of coronary arterial anatomy and distribution and severity of left ventricular wall motion abnormalities in 500 patients who underwent coronary arteriography and left ventriculography for evaluation of angina pectoris.

## Methods

The coronary arteriograms and left ventriculograms of 500 patients with coronary artery disease and angina pectoris studied between 1972 and 1977 were reviewed carefully by three physicians. When differences existed in the interpretation of this material a consensus was reached. Such differences were rare and minor in nature. Patients with coronary arterial anomalies, congenital heart disease, valvular heart disease or primary heart muscle disease were excluded. All patients had at least one lesion of greater than 50% reduction of luminal diameter in a major coronary artery.

Ninety five percent of the studies were performed percutaneously from the leg; the remainder were performed using a cutdown in the arm. The left ventriculograms were exposed on 35 mm film at 60 frames/second in the right anterior oblique projection using a Philips 11 inch cesium iodide image intensifier system (Philips Medical Systems Inc. Shelton Conn.). Only films of excellent quality and frames removed from ectop-

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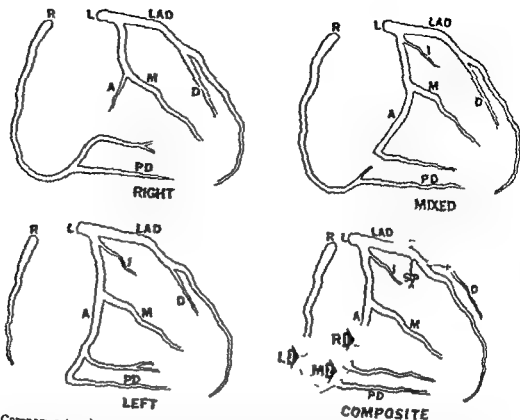


Fig 1 Coronary arterial patterns divided into Right Mixed and Left systems according to the blood supply to the L ventr surface of the left ventricle. "Breaks" in the composite diagram show how each coronary arterial pattern is formed. (P 1 = Right system M 2 = Mixed system and L 3 = Left system) Abbreviations R = right L = left LAD = left anterior descending D = diagonal SP = septal perforator I = intermediate M = marginal 4 = atrioventricular groove PD = posterior descending

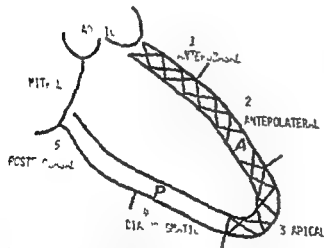


Fig 2 Left ventriculogram in the right anterior oblique projection. The left ventricle has been divided into anterior (A) and posterior (P) regions and into five areas

ic beats by at least two cardiac cycles were evaluated. Forty-five cc of Tc 99m albumin diatrizoate were introduced into the left ventricle in three seconds using a power injector. Coronary arterial patterns were divided into

Right Mixed, and Left systems depending upon the blood supply to the inferior surface of the left ventricle (Fig 1). In Right systems the right coronary artery (RCA) supplies the posterior descending artery and the posterolateral artery. In Mixed systems the RCA supplies the posterior descending artery and the atrioventricular groove artery (AV groove artery) supplies the posterolateral artery. In Left systems the RCA terminates at the acute margin of the right ventricle and the AV groove artery supplies the posterolateral artery and the posterior descending artery.

The left ventriculograms in the right anterior oblique projection were divided into five areas: (1) anterobasal (2) anterolateral (3) apical (4) posterobasal and (5) posterobasal) and two regions (anterior and posterior) (Fig 2). A scoring system was employed for each area (normal = 0 hypokinesis = 1 akinesis = 2 and dyskinesis = 3). Then the left ventriculograms were divided into four categories depending upon regional involvement: (1) normal (2) anterior dyskinesis and

Table 1 Wall motion findings by system and age ( $\pm$  standard deviation) in 500 patients with angina pectoris

	Anterior dyssynergy	Posterior dyssynergy	Anterior & posterior dyssynergy	Normal
Right system (360 pts)	49.4 $\pm$ 9.1 years 66 patients (18%)	48.8 $\pm$ 10.6 years 76 patients (19%)	50.1 $\pm$ 11.2 years 68 patients (19%)	49.5 $\pm$ 9.0 years 150 patients (42%)
Mixed system (89 pts.)	45.1 $\pm$ 8.9 years 16 patients (18%)	47.7 $\pm$ 10.2 years 14 patients (16%)	49.6 $\pm$ 10.0 years 18 patients (20%)	48.4 $\pm$ 8.1 years 41 patients (46%)
Left system (51 pts)	48.9 $\pm$ 10.1 years 17 patients (33%)	46.0 $\pm$ 3.3 years 9 patients (18%)	50.8 $\pm$ 3.9 years 8 patients (16%)	50.6 $\pm$ 10.6 years 16 patients (31%)
Total (500 pts)	48.6 $\pm$ 9.3 years 99 patients (20%)	48.3 $\pm$ 10.4 years 99 patients (20%)	49.9 $\pm$ 10.5 years 97 patients (19%)	49.5 $\pm$ 8.9 years 207 patients (41%)

(3) posterior dyssynergy alone and (4) combined anterior and posterior dyssynergy.

Statistical comparisons of mean age for each wall motion group in Table 1 with the over all mean age of all 500 patients were made by standardized Z score assuming normal age distributions and equal variances. The frequency and type of dyssynergy observed for the three coronary arterial systems (Table IV) and ages (Table V) were compared with the over all distribution of dyssynergy by contingency analysis using  $2 \times 3$  tables. The resulting Chi square with 2 degrees of freedom determined the probability of distinct differences between coronary arterial systems or decades of life.

## Results

The mean age of the 437 men was 48.5 years and the mean age of the 63 women was 53.6 years. In analyzing wall motion by coronary arterial system and age (Table I) men and women were combined. The mean age for the entire study group (49.1  $\pm$  9.61 years) was compared to each of the subcategories in Table I to determine whether either coronary arterial system or location of dyssynergic area occurred in a distinct age group. The standardized normal deviate Z was computed from the means and standard deviations of the complete group and was compared to those of the individual elements. Only in the case of Left systems did the standard deviations fall outside the expected 9 to 11 range for two categories with only nine patients (Table I). In no instance was the p value computed for differences

between means significant at the 0.05 level even for the small samples. It was concluded therefore that coronary arterial system and distribution of left ventricular dyssynergic regions are independent of age.

Table II defines left ventricular wall motion dyssynergy by coronary arterial system (Right, Mixed and Left) region (anterior dyssynergy alone, posterior dyssynergy alone or combined anterior and posterior dyssynergy) and area (1 anterobasal, 2 anterolateral, 3 apical, 4 diaphragmatic and 5 posterobasal). In all systems and regions and in all areas save apical hypokinesis was the dominant left ventricular wall motion abnormality. In case 3 (apical) dyskinesis was the dominant finding.

Patients with dyssynergy were then evaluated for extent (number of areas involved) of abnormal wall motion (Table III). In patients with anterior regional disease (anterior dyssynergy alone or combined anterior and posterior dyssynergy) areas 2 (anterolateral) and 3 (apical) together were impaired most commonly. Rarely all three anterior areas were involved. Dyssynergy was never seen in combined areas 1 and 2 or in areas 1 and 3. In posterior regional involvement the combinations of areas 4 and 5 together or area 4 alone occurred with similar frequency. It was uncommon for area 5 alone to be involved.

The frequency of occurrence of the three types of wall motion abnormality (hypokinesis, akinesis and dyskinesis) in the entire group of 500 patients (Table IV) was compared with the distribution of left ventricular dyssynergy within the

Table II Wall motion dyssynergy by system region and area

	H	A	D	Total	H	A	D
<i>Right system</i>							
<i>Anterior</i>							
Area 1	1	0	0	1	100%	0%	0%
Area 2	39	4	11	54	72%	7%	20%
Area 3	16	10	21	47	34%	21%	45%
<i>Posterior</i>							
Area 4	39	23	4	66	59%	35%	6%
Area 5	20	14	5	44	57%	32%	11%
<i>Anterior &amp; Posterior</i>							
Area 1	4	0	0	4	100%	0%	0%
Area 2	11	12	5	58	71%	21%	9%
Area 3	21	4	30	60	35%	7%	58%
Area 4	43	18	3	64	67%	28%	5%
Area 5	27	11	4	42	64%	26%	10%
Total	106	96	88	440			

*Mixed system*

<i>Anterior</i>							
Area 1	0	0	0	0	0%	0%	0%
Area 2	10	1	3	14	71%	7%	21%
Area 3	0	0	6	13	54%	0%	46%
<i>Posterior</i>							
Area 4	3	0	10	13	70%	30%	0%
Area 5	1	1	9	11	78%	11%	11%
<i>Anterior &amp; Posterior</i>							
Area 1	1	0	0	1	100%	0%	0%
Area 2	9	1	5	15	60%	7%	33%
Area 3	7	0	10	17	41%	0%	59%
Area 4	11	5	2	18	61%	28%	11%
Area 5	5	2	1	8	63%	25%	13%
Total	64	13	28	105			

*Left system*

<i>Anterior</i>							
Area 1	0	0	0	0	0%	0%	0%
Area 2	10	4	2	16	63%	25%	13%
Area 3	4	1	8	13	31%	8%	62%
<i>Posterior</i>							
Area 4	6	1	1	8	75%	13%	13%
Area 5	4	0	2	6	67%	0%	33%
<i>Anterior &amp; Posterior</i>							
Area 1	0	0	0	0	0%	0%	0%
Area 2	5	0	3	8	63%	0%	37%
Area 3	3	0	5	8	38%	0%	63%
Area 4	5	1	3	9	56%	11%	33%
Area 5	0	1	2	3	0%	33%	67%
Total	37	6	16	59			

Abbreviations: H = hypokinetic, A = ak

+ = hyperkinetic

Table III Extent of wall motion abnormalities according to coronary arterial system and degree of involvement wall motion abnormalities were divided into three categories: anterior alone, posterior alone, and combined anterior and posterior

	Right system	Mixed system	Left system	Total
<i>Anterior</i>				
Area 1 2 3	0	0	0	0
Area 1 2	0	0	0	0
Area 1 3	0	0	0	0
Area 2 3	36	11	19	66
Area 1	1	0	0	1
Area 2	18	3	4	25
Area 3	11	2	1	14
<i>Posterior</i>				
Area 4 5	34	5	5	44
Area 4	37	5	3	45
Area 5	10	4	1	15
<i>Anterior &amp; Posterior</i>				
Area 1 2 3	4	1	0	5
Area 1 2	0	0	0	0
Area 1 3	0	0	0	0
Area 2 3	47	13	1	61
Area 1	0	0	0	0
Area 2	8	1	1	10
Area 3	10	3	1	14
Area 4 5	38	8	3	49
Area 4	26	10	6	42
Area 5	4	0	0	4

three coronary arterial systems. Right and Mixed systems did not differ significantly from the over all distribution. Patients with Left systems did demonstrate a significant departure from the population as a whole ( $p < 0.05$ ) although the number of observations in this group is small. A similar analysis (Table V) was conducted for the distribution of left ventricular wall motion abnormalities according to decades of life compared with the entire population. No age group differed from the over all population (0.05 level of significance). Thus it appears that the distribution of wall motion abnormalities in patients with coronary artery disease and angina pectoris is similar from the third to the eighth decade.

Using the scoring system described in the Methods section as an index of the severity of left ventricular dyssynergy, the mean wall motion scores per patient for coronary arterial system

Table IV Comparison of wall motion findings by coronary arterial system

	H	A	D	Total score	Score per patient with dyssynergy ( $\pm$ standard deviation)/per dyssynergic area
Right systems (210 to 360 patients had dyssynergy)	256 $\times$ 1	96 $\times$ 2	88 $\times$ 3	71	3.4 $\pm$ 2.2/1.6
Mixed systems (48 of 89 patients had dyssynergy)	64 $\times$ 1	13 $\times$ 2	28 $\times$ 3	174	3.6 $\pm$ 2.5/1.7
Left systems (35 of 51 patients had dyssynergy)	37 $\times$ 1	8 $\times$ 2	26 $\times$ 3	131	3 $\pm$ 2.2/1.8
Total	357 $\times$ 1	117 $\times$ 2	142 $\times$ 3	1017	3.5 $\pm$ 2.2/1.7

For scoring purposes hypokinesis (H) = 1 akinesis (A) = 2 and dyskinesis (D) = 3

Table V Comparison of wall motion findings by decade

Decade	H	A	D	Total score	Score per patient with dyssynergy ( $\pm$ standard deviation)/per dyssynergic area	Patients without dyssynergy
20-29 (8 pts)	11 $\times$ 1	5 $\times$ 2	5 $\times$ 3	36	5.1 $\pm$ 2.5/1.7	1 (12.5%)
30-39 (80 pts)	67 $\times$ 1	14 $\times$ 2	14 $\times$ 3	132	2.6 $\pm$ 1.7/1.5	29 (36.2%)
40-49 (166 pts)	119 $\times$ 1	35 $\times$ 2	35 $\times$ 3	304	3.8 $\pm$ 1.5/1.7	73 (44.2%)
50-59 (174 pts)	113 $\times$ 1	44 $\times$ 2	49 $\times$ 3	348	3.4 $\pm$ 0.1	73 (42%)
60-69 (60 pts)	45 $\times$ 1	17 $\times$ 2	16 $\times$ 3	177	3.5 $\pm$ 2.4/1.6	29 (48.3%)
70-79 (7 pts)	7 $\times$ 1	2 $\times$ 2	3 $\times$ 3	70	4.0 $\pm$ 2.3/1.7	2 (28.6%)
Total (500 pts)	307 $\times$ 1	117 $\times$ 2	142 $\times$ 3	101	3.5 $\pm$ 2.2/1.7	207 (41.2%)

For scoring purposes hypokinesis (H) = 1 akinesis (A) = 2 and dyskinesis (D) = 3

(Table IV) and age (Table V) were compared with the mean score (3.5  $\pm$  2.2) of the entire population. None of the arterial systems had scores which differed significantly from the over all mean population ( $p > 0.1$ ). Among decades of life only patients in the fourth decade differed significantly from the mean score for the entire population. Thus there is little difference in the severity of left ventricular dyssynergy according to age.

## Discussion

The severity of coronary artery disease and the degree of left ventricular dysfunction determine the clinical presentation and natural history of patients with ischemic heart disease.<sup>2</sup> This study concentrates on a detailed description of left ventricular wall motion findings in patients with coronary artery disease and angina pectoris.

In selecting the right anterior oblique projection for analysis of the left ventriculogram the

septum and lateral wall are not seen well. However, disease confined to the septum or lateral wall is very rare. In one study of 78 separate infarctions only two infarctions were limited to the septum while three infarctions were limited to the lateral wall.<sup>4</sup> Some portion of the anterior wall is involved almost invariably in patients with septal infarction since the left anterior descending artery supplies the anterior wall of the left ventricle as well as 75% of the interventricular septum. In lateral wall infarction there is almost always anterior or posterior involvement. Thus the single plane right anterior oblique ventriculogram should be adequate for characterization and comparison of left ventricular wall motion abnormalities.

Some wall motion abnormalities are the result of ischemia and are therefore potentially reversible thereby eliminating a one to one relationship between findings at the time of left ventriculography and at autopsy.<sup>2-4</sup> However, left ventricular disease found at autopsy is commonly associated

with antemortem left ventricular dyssynergy \*

The descriptive concepts of hypokinesis, akinesis and dyskinesis have the advantages of both long term use<sup>1</sup> and wide acceptance.<sup>2</sup> The division of the left ventricle into anterior and posterior regions has been validated recently.<sup>3, 10, 11</sup>

The distribution of anterior and posterior left ventricular disease was equally divided in our population (Table I) a finding observed by others.<sup>12</sup> Combined anterior and posterior dyssynergy occurred with no greater frequency than anterior or posterior dyssynergy alone in our patients. The even distribution of regional wall motion abnormalities was not influenced by coronary arterial pattern (Tables I and IV). This is in contrast to "Langer's observations" that patients with Left systems were most vulnerable and those with Mixed systems were least vulnerable to the effects of coronary artery disease.

Hypokinesis was the most common wall motion abnormality found. This was true in all areas of the left ventricle except for area 3 (apical), where dyskinesis was found most frequently (Table II). Miller and colleagues<sup>13</sup> also noted that hypokinesis was the most common wall motion abnormality in patients with coronary artery disease.<sup>14</sup> Of their 123 patients 32% were normal 30% manifested hypokinesis 21% manifested akinesis and 17% manifested dyskinesis.

Dyssynergy occurred most commonly in adjacent areas (Table III). In patients with anterior wall dyssynergy, areas 2 (anterolateral) and 3 (apical) together were involved most commonly. This supports observations that anterior myocardial infarctions tend to be apical rather than basal in orientation.<sup>15</sup> In patients with posterior wall dyssynergy, areas 4 (diaphragmatic) and 5 (posterobasal) together were involved most frequently.

The most interesting finding in our data was the demonstration that wall motion abnormalities were similar in each decade of life studied (Table V). One might expect to find progressive deterioration of left ventricular function as one moves from younger to older patients since age is a well known risk factor for coronary artery disease. However the common denominator in this population was angina pectoris. It may be that when coronary artery disease with its attendant impact on left ventricular function expresses itself clinically, the disease is sufficiently

advanced so that any implications of age are removed.

## Conclusions

1 Forty % of patients with coronary artery disease and angina pectoris have normal left ventricular wall motion. In the 60% of patients with left ventricular dyssynergy wall motion abnormalities are divided evenly into three categories: anterior dyssynergy alone, posterior dyssynergy alone, and combined anterior and posterior dyssynergy. The mean age of patients with normal and dyssynergic wall motion is strikingly similar.

2 Coronary arterial patterns of Right Mixed and Left systems have little if any influence on left ventricular wall motion abnormalities.

3 Hypokinesis is the most common wall motion abnormality found in patients with coronary artery disease regardless of coronary arterial distribution or region of the left ventricle affected, with the exception of the apical area, where dyskinesis is found most commonly. Dyssynergy occurs most commonly in adjacent areas. In anterior wall dyssynergy the anterolateral and apical areas of the left ventricle are involved together most commonly. In posterior wall dyssynergy the diaphragmatic and posterobasal areas of the left ventricle are involved most commonly.

4 In patients with coronary artery disease and angina pectoris left ventricular dyssynergy is similar from the third to the eighth decade of life.

## Summary

Left ventriculograms of 500 patients with coronary artery disease and angina pectoris were compared with respect to coronary arterial pattern, left ventricular dyssynergy and the patient's age. The coronary arterial patterns were separated into Right Mixed and Left systems depending upon the blood supply to the inferior surface of the left ventricle. The left ventriculograms were divided into two regions and five areas. The anterior region consisted of the anterobasal area, anterolateral area and the apical area. The posterior region consisted of the diaphragmatic area and the posterobasal area. Areas were scored as normal, hypokinetic, akinetic or dykinetic. The following relationships were noted:

1 Forty percent of patients with coronary artery disease and angina pectoris have normal left ventricular wall motion. In the 60% of patients with left ventricular dyssynergy, wall motion abnormalities are divided evenly into three categories: anterior dyssynergy alone, posterior dyssynergy alone, and combined anterior and posterior dyssynergy. The mean age of patients with normal and dyssynergic wall motion is strikingly similar.

2 Coronary arterial patterns of Right Mixed and Left systems have little, if any, influence on left ventricular wall motion abnormalities.

3 Hypokinesis is the most common wall motion abnormality found in patients with coronary artery disease regardless of coronary arterial distribution or region of the left ventricle affected, with the exception of the apical area where dyskinesis is found most commonly. Dyssynergy occurs most commonly in adjacent areas. In the anterior wall dyssynergy, the anterolateral and apical areas of the left ventricle are involved together most commonly. In posterior wall dyssynergy, the diaphragmatic and posterobasal areas of the left ventricle are involved most commonly.

4 In patients with coronary artery disease and angina pectoris, left ventricular dyssynergy is similar from the third to the eighth decade of life.

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# Effects of induced psychological stress on click and rhythm in mitral valve prolapse

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The variability of auscultatory findings in patients with mitral valve prolapse (MVP) has been extensively studied. Changes in the timing of the click and murmur on a repeat examination and with respiration and other physiologic (e.g. sitting, standing, squatting, Valsalva maneuver) and pharmacologic (e.g. amyl nitrite pressors) maneuvers have received considerable attention. However, a few studies have also examined the amplitude of the click in a similar fashion. Our clinical observations suggested that anxiety tended to accentuate the click in patients with MVP. The present study was designed to examine the effects of anxiety on the auscultatory features of MVP. In addition, since atrial and ventricular rhythm disturbances are common in this condition,<sup>1</sup> it was hypothesized that anxiety might exacerbate these dysrhythmias. Thus, during the administration of acute psychological stress designed to induce anxiety, the rhythm was monitored and the phonocardiogram (PCG) was recorded. This preliminary report shows that some patients with the systolic click murmur syndrome are profoundly affected by such a stress.

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## Materials and methods

The present study group was composed of 30 subjects—15 patients and 15 controls. All patients had clinical features of the systolic click murmur syndrome. Each patient had auscultatory evidence (confirmed by phonocardiography) of a late systolic click which varied in timing with the bedside maneuvers designed to change ventricular volume. All had been studied by echocardiography and MVP was confirmed in 11 patients. The four patients without echocardiographic confirmation had the characteristic auscultatory features. None had evidence of other cardiac disease. The control subjects matched by age and sex had no evidence of heart disease.

Informed consent was obtained prior to the study. As shown in Fig 1, subjects remained semirecumbent in an easy chair during the entire study. A single electrocardiographic (ECG) lead was continuously monitored. A microphone was placed over the cardiac apex where sounds were best recorded. The microphone was secured to the chest with a rubber strap and tape so that it was held motionless throughout the experiment. All ECG and PCG recordings were made on a Cambridge multichannel recorder. The sound recordings were made after filtration through a 100 to 250 Hz high pass filter with 24 db per octave roll off. Once set, the controls were not changed during the entire study. The paper speed for continuous recording was 5 mm/second and was increased to 50 mm/second for ten to 15 seconds at the end of each minute. Thus, the rhythm could be evaluated continuously throughout the



Fig 1 Subject shown viewing slide projector (for amplification see text)

experiment and the amplitude and timing of the click could be analyzed each minute during the fast paper speed

A rest period was followed by three different tests periods (practice Task I Task II). The three test periods constituted the psychological stress which was deemed to be sufficiently intense for experimental purposes while still within ethical boundaries. Patient anxiety was assessed at three points in the study—After rest after Task I and after Task II. The State Trait Anxiety Inventory (STAI) developed by Spielberger and associates<sup>18</sup> was employed for this. During the rest period the subjects lay quietly. During the test periods several guessing tasks were administered on a Singer Caramate slide projector. During the initial explanation of the test in an effort to intensify the anxiety response it was implied that the accuracy of sequence guessing is a measure of intelligence. In each of the three tests the subject was asked to recognize and retain a sequence of the letters X and O which was repeatedly projected. The sequence for each test is illustrated in Fig 2. A letter was projected and then removed from the screen. When the letter was removed the subject was expected to guess the next letter. A correct response was predicated on recognition and memorization of the sequence. The responses were recorded on the Cambridge multichannel recorder with hand held buttons marked X and O and therefore no talking was required.

## RECURRING LETTER SEQUENCE IN THE THREE TESTS

Practice	XXOO
Task I	XOOO
Task II	O X O O X O X O X O X X O X O O X X O X

Fig 2 Recurring letter sequence in the three tests.

During the practice test slides were advanced manually and this period was used to familiarize the subject with the testing technique. Practice was terminated when the subject accurately guessed eight consecutive letters. In Task I and Task II the slides were advanced automatically at a preset rate. Task I was terminated after eight consecutive correct guesses. Task II the 20 letter sequence which was essentially unachievable was projected three times—and no subject mastered the pattern. The average total duration of each test which included both explanation and actual testing was: rest—7 minutes (range 5 to 11 minutes); practice—5 minutes (range 2 to 13 minutes); Task I—6 minutes (range 3 to 9 minutes); and Task II—9 minutes (range 7 to 13 minutes).

The STAI administered during the study is composed of two separate subjective scales for measuring two distinct anxiety concepts. The



Table I Patients

Patient	Age	Sex	N.E.X	S.M	Prolapse on echo	Drugs	Rhythm change during test	X ch. dur. test
<b>Group A</b>								
J F	45	F	+	+	Yes	Prop 80 qd.	New multifocal VEBs	Increase
E C	41	F	+	+	No	None	New CSR	Increase
L W	49	F	+	+	Yes	None	New VEBs	Increase
J W	18	F	+	—	Yes	None	New multifocal VEBs	Increase
M A	51	M	+	+	Yes	None	Increased VEBs	No
I G	37	M	+	—	No	None	No	Increase
<b>Group B</b>								
N G	25	F	+	+	Yes	None	No	Decrease
S F	57	M	+	+	Yes	None	No	Decrease
S D	36	F	+	+	Yes	Quinidine 800 qd	No	No
T Y	32	F	+	—	Yes	Prop 160 qd	No	No
T M	32	F	+	—	No	Prop 80 qd	No	No
P C	41	F	+	+	Yes	Prop 20 qd	No	No
						Meprobamate 200 qd		
I W	52	F	+	+	Yes	None	No	No
F B	49	M	+	—	Yes	None	No	No
L B	25	F	+	—	No	None	No	No

Table II Heart rates (Average  $\pm$  SEM)

	Rest	Practice	Task I	Task II
All patients (17)	72.27 $\pm$ 44	76.13 $\pm$ 51	78.90 $\pm$ 48	88.57 $\pm$ 58
Group A patients (6)	74.58 $\pm$ 88	80.62 $\pm$ 98	84.85 $\pm$ 96	83.85 $\pm$ 90
Group B patients (9)	69.06 $\pm$ 45	73.14 $\pm$ 56	75.01 $\pm$ 54	85.56 $\pm$ 61
Controls (15)	75.50 $\pm$ 48	80.74 $\pm$ 56	82.33 $\pm$ 53	81.38 $\pm$ 58

A Trait scale consists of 20 questions about the subject's general level of anxiety. The A State scale consists of 20 questions designed to indicate a subject's level of anxiety at a given moment in time. Both were given after rest and then A State was given alone after Task I and Task II.

The subjects were debriefed on completion of the study, emphasizing that they were not expected to correctly guess the sequence of Task II. They were then told that the purpose of the tests had been to create psychological stress with a frustrating experience. The entire study was completed in 30 to 45 minutes.

From the continuously recorded single lead ECG the rhythm was analyzed over each one minute period and arrhythmias were noted. If ventricular ectopic beats (VEBs) were observed their frequency was reported each minute as a projected rate per 1000 heart beats. For each of the four periods (rest, practice, Task I and Task II) a mean of these minute values for VEB

frequency was computed. The rhythm during rest was compared to that of each of the three test periods.

At the end of each minute during the faster paper speed (50 mm/sec) the RR interval over five consecutive cycles was averaged to compute the heart rate. In addition, amplitude of the click was measured during the fast paper speed. The amplitude for a given minute was obtained by averaging the clicks in five consecutive beats. All VEBs and post ectopic beats were excluded from analysis of the clicks. In addition, clicks were not analyzed when obscured by patient noise (talking, movement, deep breathing). Thus, during some minutes no value for amplitude of the click was available. Any gross change in timing of the click was also noted. The amplitude during rest was compared to that of each of the three test periods. A click was considered to have changed if its amplitude during a test period differed from its amplitude during rest by 50% or more.

Table III State anxiety scores (Average  $\pm$  SEM)

	Post rest	Post Task I	Post Task II
All patients (15)	33 $\pm$ 2.1	36 $\pm$ 2.6	41 $\pm$ 2.1
Group A patients (6)	36 $\pm$ 3.6	34 $\pm$ 3.6	39 $\pm$ 2.7
Group B patients (9)	32 $\pm$ 2.5	37 $\pm$ 3.6	42 $\pm$ 3.2
Controls (15)	29 $\pm$ 1.0	33 $\pm$ 2.2	39 $\pm$ 2.4

Statistical evaluations were made using chi square analyses and two tailed  $t$  tests

### Results

Patient characteristics are outlined in Table I. There were 11 females and four males with a mean age of 39 years (range 18 to 57 years). The controls were comparable with the same sex distribution and a mean age of 40 years (range 21 to 54 years).

Patients were separated into two groups depending on their response to the psychological stress. In Group A are six patients who showed either a change in rhythm and/or an increase in amplitude of the click from the rest to a test period. Group B is composed of nine patients who showed no change in rhythm and in whom the click did not increase in amplitude.

The cardiac rhythm changed during nine test periods in five of 15 patients. The arrhythmias consisted of new VEBs in three, increased VEBs in one, and a new AV nodal (junctional) rhythm in one. In the four patients with VEBs the frequency changed from rest period values of 0/0 and 173 (VEBs/1000 beats) to test period values of 4/18, 277 and 312 respectively. No control subject had a rhythm disturbance during administration of the test ( $p < 0.05$  by chi square test), and the only arrhythmia noted in this group was a single VEB in one subject during rest.

Fig 3 illustrates the changes in amplitude of the clicks in individual patients. As shown, the click increased by 50% or more in five patients in Group A, and decreased by this amount in two of the Group B patients.

Heart rate data are depicted in Table II. In all groups there was an increase in heart rate from rest to the test periods, but this was not statistically significant. The heart rates of Group A patients increased more than those of Group B patients and controls, but these differences did not approach significance.

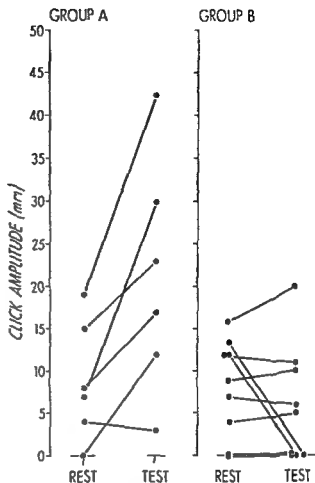


Fig 3 Changes in amplitude of the click in individual patients

Average A Trait scores were similar for all groups ( $\pm$  SEM). Group A = 35.5  $\pm$  2.46, Group B = 35.3  $\pm$  1.51, controls = 35.7  $\pm$  7.12. The A State scores are displayed in Table III. The post rest scores for patients were higher than for the controls ( $p < 0.05$ ). The post rest scores for Group A and Group B were not significantly different, although the group A scores were higher than those of controls ( $p < 0.05$ ), whereas Group B scores were not. The scores after Task I and Task II were similar for all groups.

For both the patients and control subjects there was an increase in A State score from post rest to post Task II ( $p < 0.001$ ). The increase for Group B was significant ( $p < 0.001$ ). The higher initial anxiety score in Group A showed no significant further increase, although these patients reported the highest average State anxiety after Task II.

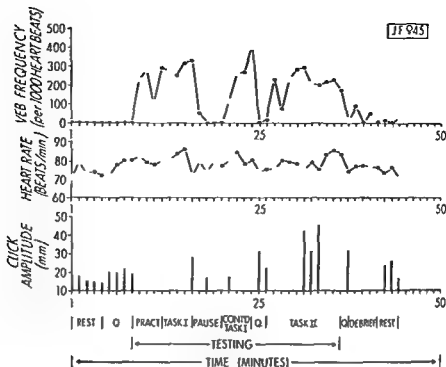


Fig 4 Response of patient J F to the psychological stress

One patient J F demonstrated a dramatic change in rhythm and click which paralleled the periods of psychological stress. The details of this study are outlined in Fig 4. Of particular note is the occurrence of rhythm disturbance almost exclusively during administration of the test with a rapid return to baseline during interruptions. The VEBs were multifocal and bifurcated couplets were noted from one to seven times per minute during the tests. The patient is a forty two year old female with a mid systolic click and late systolic murmur T wave inversions in Leads II, III, AV<sub>F</sub>, V<sub>1</sub> on the resting ECG and classical MVP on echocardiogram. She was the only patient in this series with the auscultatory electrocardiographic variant of the systolic click murmur syndrome. At selective angiography, normal coronary arteries had been demonstrated.

#### Discussion

This study suggests that acute psychological stress exerts a significant effect on the rhythm and click in some patients with MVP. It is proposed that these changes are related to the anxiety and frustration induced by the guessing tests.

The click is known to change in both timing

and intensity under a variety of circumstances. Its presence may vary from one examination to the next<sup>2</sup> but this phenomenon has not been systematically evaluated. In some the click is noted in only one phase of respiration either in inspiration<sup>4</sup> or expiration<sup>2,4</sup>. Click changes related to posture are well known.<sup>7,10,14,16</sup> The click occurs earlier in systole on the patient assuming an upright posture. If the click is absent in the supine position it may appear with the patient upright. Amyl nitrite administration also affects the click<sup>2,4,5,6,8,10,16</sup> consistently occurring earlier with a variable effect on the amplitude. Recently Towne and colleagues<sup>12</sup> have examined the effects of tachycardia induced by right atrial pacing. The click occurred earlier in systole as pacing rates were increased. Click amplitude in most subjects was unchanged or decreased as the heart rate increased but in others the click appeared only at more rapid rates (above 120/minute). The administration of pressor agents (phenylephrine and metaraminol) also affects the click<sup>11</sup> with its timing generally moving later in systole and with a variable effect on amplitude. The effects of psychological stress and/or anxiety on the click have not to the best of our knowledge been previously reported.

In the present study the amplitude of the click

increased during psychological stress in five of 15 patients. In one of the five the click also occurred earlier and in another it occurred later in systole. Click amplitude decreased during stress in two patients.

Patients with MVP are known to exhibit a variety of atrial and ventricular rhythm disturbances more frequently than do normals.<sup>7</sup> Sudden death rarely occurs and may be related to ventricular tachyarrhythmias.<sup>21</sup> Although the effects of psychological stress and/or anxiety have not been examined in MVP patients, Lown and colleagues<sup>22</sup> extensively studied a patient without evidence of organic heart disease in whom VEBs were provoked by psychological stress.

In five of our 15 patients a new arrhythmia developed during psychological stress or an existing arrhythmia was accentuated. This contrasts with the controls who exhibited no rhythm disturbances during psychological stress. The arrhythmias consisted of new VEBs in three, increased VEBs in one, and new coronary sinus rhythm in one. In one of our patients the only one with auscultatory-electrocardiographic variant a serious ventricular arrhythmia was consistently provoked by psychological stress.

It is tempting to speculate that the rhythm changes and increased amplitude of the click seen in these patients are anxiety related. A possibility remains that an increased amplitude of the click may be random and could reflect the natural variability of the click in this disorder. However, such spontaneous short term variability has not been documented. Postural effects were not involved as the patients remained in one position. Since five consecutive cardiac cycles were examined, respiratory variations are unlikely to have played a role. It is postulated that the mechanism by which anxiety alters the click and the rhythm is an increase in sympathetic nervous system tone. Increased sympathetic tone with augmentation in contractility may cause an accelerated rate of ejection. The click occurs during ejection at or near maximal valve prolapse and is ascribed to abrupt tensing of leaflets and chordae.<sup>2,3</sup> An increased rate of left ventricular ejection at the time of the leaflet prolapse might be expected to accentuate the click and there is some evidence to support this concept. The click could also be affected by alterations in heart rate and

blood pressure secondary to increased sympathetic tone. Our subjects showed a small (and non significant) increase in heart rate during the test and three of the five patients with increased click developed tachycardia (maximum being 103 beats/minute). However, the evidence from pacing studies suggests that such alterations in rate should be associated with minimal if any change in the click. Blood pressure was not continuously recorded during the study. The risks and discomfort of intra arterial pressure measurement were not considered justifiable in this study of generally well outpatient volunteers. Blood pressure measurement by cuff would have interfered with subjects' concentration during testing and hence was not obtained. An increase in blood pressure during the anxiety stress may also explain the finding of increased click amplitude. The rhythm change in our patients may be secondary to sympathetic nervous system effect on automaticity.

A particularly interesting feature of our study concerns the only patient with the auscultatory-electrocardiographic variant whose behavior during psychological stress may provide some insight into a potential mechanism of sudden death in this group of patients. Recent reports<sup>23</sup> suggest that MVP patients with the auscultatory-electrocardiographic variant may have a higher risk of sudden death. The mechanism of sudden death in these patients could be related to anxiety induced arrhythmias. In another report MVP patients who had experienced ventricular fibrillation were studied to ascertain factors which might increase ventricular ectopy.<sup>24</sup> A variety of physiologic and pharmacologic interventions were employed without success, but psychological stress was not used. The striking response of our patient suggests that further investigation into the effects of psychological stress in a similar subset of patients may be valuable. Additional work to confirm these observations and to elucidate the mechanism underlying the observed rhythm and click changes (e.g. administration of isoproterenol) will provide a better understanding of arrhythmias in this common syndrome. The findings in the present study may explain the commonly noted variability in auscultatory findings in MVP patients. If anxiety does indeed precipitate rhythm disturbances, routine psychological stress testing might help to identify those in whom

certain interventions (e.g. behavioral modifications, psychotherapy, tranquilizers) could be therapeutic.

## Summary

Our clinical observations suggested that anxiety accentuated the click in patients with mitral valve prolapse. In order to evaluate this systematically, a psychological stress was administered to 30 subjects—15 patients with click murmur syndrome and 15 normal controls. The phonocardiogram was recorded and the electrocardiogram were continuously monitored to assess the effects on arrhythmias.

State Anxiety Inventory scores demonstrated an increase in anxiety during the psychological stress. A change in rhythm during psychological stress was noted in five of the 15 patients. No arrhythmias occurred in the control subjects during psychological stress ( $p < 0.05$ ). Amplitude of the click increased during psychological stress in five of the 15 patients, in four associated with arrhythmia.

The only patient with auscultatory electrocardiographic variant developed frequent multifocal ventricular ectopics with couplets during the psychological stress.

Acute psychological stress exerts important effects on the rhythm and click only in some patients with mitral valve prolapse and may provide a mechanism for intermittence of clicks and episodes of profound unexplained arrhythmias.

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## Newly developed systolic murmur in patients with a transvenous pacemaker

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It is important that physicians of all disciplines become aware of the variations in heart sounds and murmurs that may be encountered in patients with endocardiac pacemakers. When a newly developed systolic murmur is observed in a patient with an artificial pacemaker serious complications should be suspected such as rupture of the papillary muscle chordae tendineae and interventricular septum (IVS). However it should be borne in mind that such newly developed systolic murmurs can be observed in patients with any complications due to the artificial pacemaker.

We report 14 patients in whom a transvenous cardiac pacemaker produced a systolic musical murmur in the absence of any complications.

### Case reports

**Case 1** A 73 year old man was admitted to Kyorin University Hospital due to a recent syncope attack. An electrocardiogram (ECG) taken on admission indicated right bundle branch block (RBBB) with left axis deviation (LAD) which was consistent with a bifascicular block. Precordial examinations on admission disclosed a normal first heart sound the second sound was physiologically split the third sound was not heard. No systolic clicks were heard. Prolongation of the H-V interval (78 msec) was observed on the His bundle electrocardiogram. Then as a

safety precaution for further investigation, a temporary transvenous pacemaker was inserted via the right external jugular vein and was positioned in what was judged to be the apex of the right ventricle (RV). A high pitched systolic murmur suddenly appeared when the pacing was turned off. The murmur persisted for several minutes after pacing off and then spontaneously disappeared (Fig 1). The same auscultatory phenomenon was observed each time the pacemaker was switched off. Switching on the pacemaker resulted in the simultaneous phonocardiographic disappearance of the systolic murmur. A chest roentgenogram showed that the catheter tip was correctly positioned in the right ventricular apex. There were no clinical findings suggestive of rupture of the papillary muscle chordae tendineae, ventricular perforation or twitching of the diaphragm.

**Case 2** A 68 year old man was referred to Kyorin University Hospital for evaluation due to shortness of breath and general fatigability. On admission his pulse rate was 46/minute. An ECG revealed sinus bradycardia. A diagnosis of sick sinus syndrome (SSS) was established by over drive suppression tests which indicated prolongation of the sinus nodal recovery time (68 sec). A temporary transvenous pacemaker was inserted. No specific murmur was auscultated when the pacing was turned off immediately after insertion of the pacemaker. On the next day however a high pitched systolic murmur or so called "musical systolic murmur" was heard at the cardiac apex when the pacing was turned off (Fig 2). From then on the murmur consistently appeared at each instant the pacemaker was being turned off. A chest roentgenogram showed no myocardial

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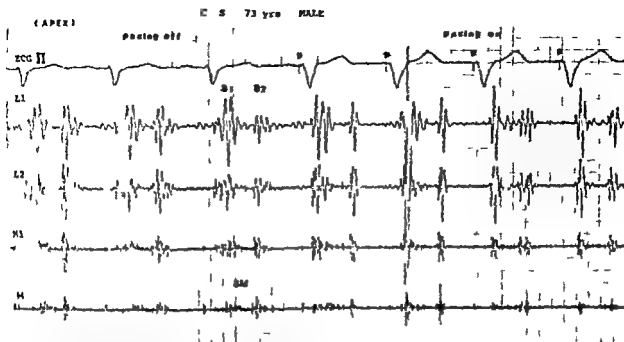


Fig 1 Phonocardiogram in Case 1 With the pacing off a diamond shaped murmur appeared in the mid-systolic period and with the pacing on (this murmur disappeared). Abbreviations P pacemaker artifact S<sub>1</sub> The first heart sound S<sub>2</sub> the second heart sound SM systolic murmur

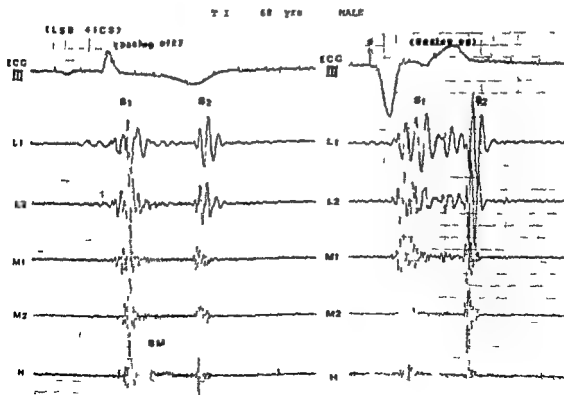


Fig 2 Phonocardiogram in Case 2 With the pacing off a high pitched systolic murmur was observed. With the pacing on the high pitched murmur was apparently diminished and the low pitched vibrations were intensified.



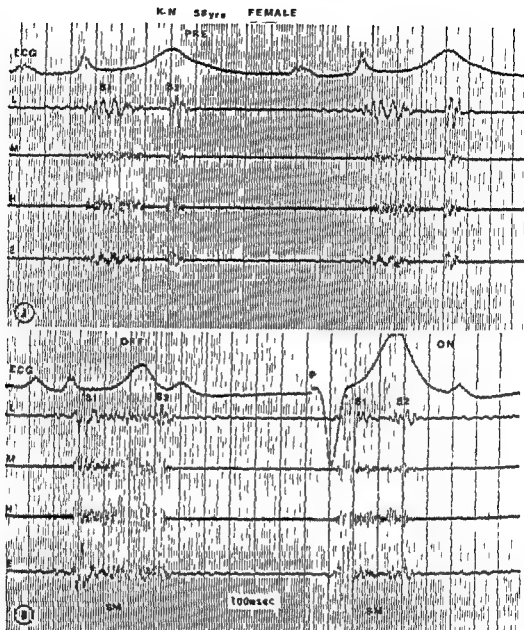


Fig 3 Phonocardiogram in Case 3 A Before pacemaker placement an early systolic murmur was observed B After pacemaker placement a high pitched murmur appeared in the mid and late systolic phases which was apparently different in quality and intensity from that observed before pacemaker placement

perforation or displacement of the pacemaker catheter. Fluoroscopy revealed no unusual movement of the left hemidiaphragm. Echocardiograms revealed no evidence of rupture of the chorda tendineae or papillary muscle.

**Case 3** A 58 year old woman was hospitalized due to dizziness and precordial pain. An ECG revealed complete heart block with a ventricular rate of 42/minute. A temporary transvenous pacemaker was inserted. On turning the pacing off a high pitched musical systolic murmur appeared which was apparently different in

intensity and quality from the murmur which had been recorded before pacemaker insertion (Fig 3). This murmur was not audible when the pacemaker was being turned on. A chest x ray, echocardiogram and physical examination revealed no evidence of serious complications.

**Case 4** A 58 year old woman was admitted to Kyorin University due to palpitations and dizziness. On admission her pulse rate was 43/minute and was irregular. An ECG revealed sinus bradycardia and sinus arrhythmia. Marked cardiomegaly (cardiothoracic ratio 63%) was observed on

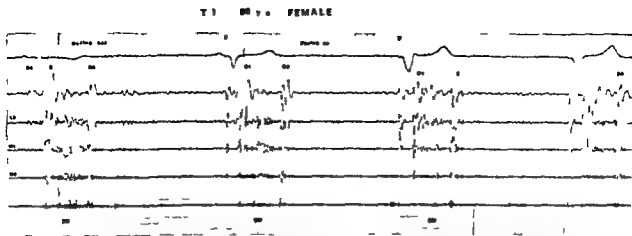


Fig 4 Phonocardiogram in Case 4 With the pacing off a high pitched systolic murmur (fishbone murmur) with its peak in the mid-systolic period was observed. In the first beat after turning the pacing on no evident change was observed except for a decrease in the loudness of the murmur. In the second beat and thereafter the systolic murmur was converted to a low pitched murmur and decreased in intensity.

her chest x ray. A grade 2/6 systolic murmur was auscultated in Erb's area. Prolongation of the sinus nodal recovery time (3.4 sec) was found. A temporary pacemaker was therefore inserted. No specific murmur was heard when the pacing was turned off immediately after insertion of the pacemaker. However, on the following day a systolic musical murmur appeared which was apparently different in quality from that recorded before pacemaker insertion. No physical or fluoroscopic signs of twitching diaphragm or intercostal muscle were seen. Furthermore, there were no clinical or echocardiographic findings suggestive of serious complications such as rupture of the chorda tendineae or papillary muscle or ventricular perforation.

## Discussion

There have been several reports regarding the new development of heart murmur generated by insertion of transvenous catheter.<sup>1-3</sup> The most common auscultatory finding in association with a transvenous pacemaker is a presystolic click (pacemaker click) which was first described by Nager and associates<sup>2</sup> who considered it to be of cardiac origin. However, subsequent studies have revealed that it is largely related to direct stimulation of the intercostal muscle or the diaphragm by a catheter electrode.<sup>4</sup> Recently Isner and co-workers<sup>5</sup> suggested that the pacemaker click resulted from crisp contact of the catheter against the ventricular septum. A presystolic click in a patient with an artificial pacemaker is generally

considered to be an insignificant auscultatory finding although it may rarely be indicative of silent myocardial perforation or partial penetration into the right ventricular myocardium. In none of our four patients, however, was a pacemaker click observed. Beside cardiac pacing with a transvenous catheter has become a widely used technique. Yet in spite of the frequency with which this procedure is employed, catheter-induced cardiac murmur is apparently very unusual. Why a rare auscultatory abnormality occurred in our patients remains to be established.

Although the exact mechanism of production of the systolic murmur which we observed is not clearly understood, we considered three possibilities as follows:

1. The systolic murmur might represent tricuspid insufficiency induced by the insertion of the cardiac electrode in the RV. Nachamki and associates<sup>6</sup> noted three patients with a systolic click and late systolic murmur described as superficial and scratchy sounding. Two of the three murmurs increased in intensity with inspiration. They postulated that the murmur represented tricuspid insufficiency caused by mechanical interference with tricuspid valve closure. This hypothesis, however, seems to be less likely in our cases since the systolic murmur was of the ejection type, not a regurgitant one, and its intensity was not increased with inspiration. Furthermore, with this hypothesis it would be difficult to explain why the systolic murmur in our

cases appeared only when the cardiac pacing was being cut off

2 The systolic murmur might be attributable to endocardial friction rubs. Recently Glassman and co-workers<sup>9</sup> reported two cases having typical sounds of cardiac friction rub after placement of a temporary transvenous pacemaker. They postulated that the cardiac murmur might have resulted from endocardial friction rubs due to contact of the pacing wire with the inner surface of the myocardium. Like a pericardial friction rub the endocardial rub was also audible during the systolic and diastolic phases of the cardiac cycle. Although our cases showed only a systolic murmur, the phonocardiographic pattern of the systolic murmur in them revealed a rather close resemblance to that of the endocardial friction rub reported by Glass and associates.<sup>9</sup> A further confirmation of our findings is therefore that pacing off could create a more suitable situation for the production of an endocardial friction rub.

3 The systolic murmur might be generated by vibration of the pacing electrode in the RV. Costeas and associates<sup>1</sup> reported the new development of sounds and murmurs after insertion of a cardiac pacemaker which they called systolic cardiac whoop. They attributed these auscultatory phenomena to movement of the pacing wire in the RV. If we consider the systolic murmur in our cases on the basis of such cardiac whoop, the question again arises as to why the systolic murmur occurred only when the pacing was being cut off. Although an exact answer cannot be given, the production of the systolic murmur in our cases could possibly have arisen from sudden pacing off altering the manner of myocardial contraction and generating a great change in blood flow in the right ventricular cavity, which could also lead to the right ventricular cavity becoming a resonant chamber.

### Conclusion

The finding of a pacemaker induced cardiac murmur in patients with transvenous pacemakers should be followed by a search for serious complications such as rupture of the interventricular

septum, chordae tendineae, or papillary muscle. Whatever the genesis of this murmur may be, it should be remembered, however, that the present results show a systolic murmur may be newly developed due to no apparent cause in patients with artificial pacemakers.

### Summary

We encountered four cases in which a transvenous cardiac pacemaker produced a systolic musical murmur in the absence of any complications. This systolic murmur appeared only when the pacing was being cut off and disappeared soon after the pacing had been turned on. Although the exact mechanism of production of the murmur remains uncertain, several possible mechanisms for its occurrence are discussed. It is apparent from this study that a systolic murmur can newly occur without any obvious cause in patients with a transvenous pacemaker.

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# Experimental and laboratory reports

## Left ventricular function in severe pure mitral stenosis as seen at the Kenyatta National Hospital

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In Kenya as in other developing areas<sup>1,2</sup> it has long been the clinical impression that rheumatic heart disease follows an accelerated course with established valvular lesions presenting at a very young age. This study was undertaken to evaluate this impression hemodynamically and to determine whether this rapid progression in endocardial involvement is paralleled by a similar involvement of the myocardium. The model of pure mitral stenosis was used so as to obviate the possibility of left ventricular dilatation being the cause of left ventricular dysfunction.

Abnormal left ventricular function in mitral stenosis has been discussed extensively in the western literature.<sup>3-5</sup> By studying left ventricular function in this young age group and its change with advancing age we hoped to further elucidate the cause of the left ventricular dysfunction.

### Materials and methods

Twenty one consecutive Black African Kenyans with pure mitral stenosis underwent hemo-

dynamic investigations at the Kenyatta National Hospital. These patients were studied at an altitude of 5 400 feet and most lived at approximately this altitude. Patients with coexistent aortic valve disease as determined by pullback pressure recordings and supra-valvular injection or any but the most minimal mitral incompetence were excluded from this study. None of the patients showed any clinical evidence of active rheumatic heart disease. The age range was 6 to 50 years with a mean and standard error of  $22.9 \pm 9.6$  years. There were 15 females and six males. Six patients were in atrial fibrillation and the remainder were in sinus rhythm.

All patients were studied in the fasting state with meperidine and/or diazepam sedation. Right and retrograde left heart catheterization were performed in all patients with additional trans-septal catheterization in four. Cardiac output was determined by the direct Fick principle with oxygen consumption being measured by a Collins spirometer. The valve area was calculated by the Gorlin formula.<sup>6</sup> An adequate wedge or left atrial pressure could not be obtained in six patients with severe pulmonary hypertension.

After pressure recordings and cardiac output determination all patients underwent left ventricular cineangiography in the right anterior oblique projection followed by a supra-valvular aortic root injection. Left ventricular cineangiography was performed with the injection of 1 ml/kg of Urographin 76 at 15 ml/sec by a volume injector\* and recorded on 16 mm film at

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Fig 1 Illustrative cineangiogram of left ventricle A End-diastolic volume = 83 ml/M B End systolic volume = 48 ml/M

hemodynamic quantitation of the severity of mitral stenosis. Combining three series where hemodynamic data is available (Table III), the mean age was  $44.3 \pm 12.1$  compared to  $22.9 \pm 9.6$  in our series ( $p < 0.001$ ). As can be seen from the mitral valve indices and mean pulmonary artery pressures, our patient population is comparable with regard to the severity of the disease.

This study also demonstrates that the effects of the rheumatic process in mitral stenosis are not limited to the endocardium but also involve the myocardium. There was significant impairment of the ejection fraction, with half of the subjects having values below two standard deviations of the accepted mean. This marked diminution in ejection fraction is greater than that described by most authors in western countries and is presumably indicative of a more virulent disease in our population.

It however must be borne in mind that inci-

dence studies of rheumatic mitral stenosis are not available in Kenya. Patients are seldom seen in our clinic except if they present or are referred with a complaint. Mass screening and routine physical examinations are still a rarity. It may well be therefore that our patient population represents the severe end of a spectrum of disease. This may in part explain the marked severity of both endocardial and myocardial involvement. The marked pulmonary hypertension and increased pulmonary vascular resistance may also be influenced by the altitude ( $> 5000$  feet) at which most of our patients live and where all were studied.

Left ventricular dysfunction in mitral stenosis was postulated originally on the basis of post-mortem findings<sup>2, 11</sup> and in the last decade has been confirmed in the hemodynamic laboratory by several investigators.<sup>12-14</sup> This decrease in performance of the left ventricle is a commonly suspected

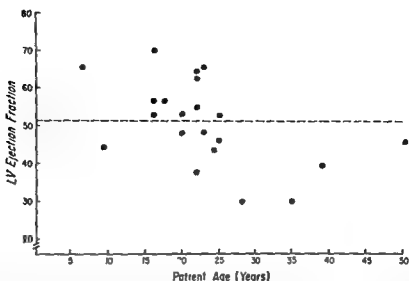


Fig 2 Left ventricular ejection fraction related to age in 21 patients with mitral stenosis. The dashed line represents the lower limit of normal by the criteria of Kennedy, et al. The ejection fraction was abnormally low in 10 patients and the ejection fraction was significantly lower with increasing age.

Table III

Series	Number	Mean age (years)	Mitral valve index (cm <sup>2</sup> /M <sup>2</sup> )	Mean pulmonary artery pressure (mm. Hg)
Holtzer et al.	10	37.9	0.48	34
Curry et al.	12	40.9	0.60	32
Heller et al.	25	46.1	0.62	42
Cumulative	47	44.3 ± 12.1	0.64	35
Present series	21	29.9 ± 9.6	0.60	50

use of poor surgical results in patients treated with both commissurotomy<sup>8</sup> and valve replacement.<sup>2,23</sup>

The etiology of left ventricular dysfunction in severe mitral stenosis remains controversial. Despite the young age of the study group we do not believe that the decreased ejection fraction observed represented an acute carditis at the time of catheterization since patients with active rheumatic fever were excluded by protocol.

Furthermore, if acute carditis were an important factor it would be expected that the most severe impairment would be in the youngest patients, i.e. those most likely to have active disease. However, myocardial performance significantly decreased with increasing age. Our data are also inconsistent with the thesis that decreased preload plays a significant role. In fact, the end-diastolic volume tended to be higher than the accepted normal values ( $0.05 < p < 0.1$ ). This

slight increase in end diastolic volume may represent compensatory dilatation.

Heller and Carleton<sup>24</sup> suggested that the rigid mitral complex results in decreased contractility of the posterobasal area accounting for the diminished ejection fraction. Contraction plots in our patients, however, did not show the myocardial abnormality to be limited to this area but as others have found<sup>25</sup> the decreased contractility was generalized.

Another commonly suggested cause is the coexistence of ischemic heart disease. Several authors have suggested that arteriosclerotic coronary artery disease is the most frequently found abnormality associated with myocardial dysfunction in valvular heart disease.<sup>26,27</sup> The patient population in this study was far too young ( $22.0 \pm 0.6$  years with 81% under the age of 25) to implicate coronary artery disease as the cause of left ventricular dysfunction. Furthermore, ischemic heart

disease in Africans at the Kenyatta National Hospital is exceedingly rare

It is of interest that myocardial involvement did not parallel that of the endocardium as there was no correlation between the ejection fraction, mitral valve area or any other hemodynamic index of severity. However, there was significant deterioration of left ventricular function with age despite there being no evidence of continued deterioration in already established severe mitral stenosis. This would suggest that in our patient population myocardial deterioration is an ongoing and slower process in contrast to the early and severe endocardial involvement.

Significant myocardial involvement accompanies the early severe endocardial lesion of young patients with mitral stenosis in Kenya and perhaps in other developing countries. The diffuse nature of the process as well as its lack of association with large and medium coronary artery disease suggests that it is a result of a diffuse myocarditis or vasculitis at the time of the initial attack of acute rheumatic fever. The deterioration of left ventricular function with time we interpret as the resolution of the acute inflammatory process with development of diffuse or localized fibrosis of the myocardium and/or diffuse occlusive vasculitis, both of which have been noted pathologically.<sup>22</sup>

## Summary

Twenty-one consecutive Black African patients with severe pure mitral stenosis were evaluated hemodynamically. It was found that advanced mitral stenosis presents itself in Kenya at a very young age ( $22.9 \pm 9.6$  years, mean  $\pm$  SD) with all but three patients under thirty. Left ventricular angiography demonstrated significant impairment of left ventricular function with 50% of patients having abnormally low values (mean ejection fraction  $0.50 \pm 0.11$ ). This diminished ejection fraction was related primarily to diffuse hypokinesia and an increased end systolic volume. There was a significant deterioration of ejection fraction with increasing age which could not be correlated to increased severity of mitral stenosis or pulmonary hypertension. It is proposed that the diffuse nature of the myocardial involvement and its progression with age in a young population without coronary artery disease represents the resolution of the acute inflammatory process of rheumatic fever to a diffuse fibrosis of the myocardium and an occlusive vasculitis.

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# Therapeutic indices for transchest defibrillator shocks Effective, damaging and lethal electrical doses

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Ventricular defibrillation by an electric shock applied across the chest is a lifesaving but not necessarily innocuous clinical procedure. Animal studies have demonstrated both morphologic damage and functional impairment of the heart following defibrillator shocks.<sup>1-6</sup> Indirect evidence for shock induced myocardial damage in man includes ECG changes,<sup>7</sup> elevated cardiac isoenzyme levels in plasma,<sup>8</sup> and positive scintigrams.<sup>9</sup> In order to prescribe the safest and most effective electrical dose for defibrillation knowledge of the margin of safety for defibrillator shocks is required. The classical pharmacologic measure of the margin of safety of a drug is the therapeutic index which may be defined as the ratio of either the median toxic or the median lethal dose to the median effective dose. Because harmful effects cannot be intentionally induced in human subjects it is necessary to consider this relationship between effective and damaging electrical doses in experimental animals. The present study establishes therapeutic indices for single damped sine wave defibrillator shocks in dogs.

## Methods

The experimental defibrillator. Investigation of the therapeutic and damaging effects of single damped sine wave shocks were conducted with our experimental high energy defibrillator.<sup>1</sup> The energy storage capacitor of this device could be varied from 0 to 100 microfarad, the series inductance could be varied from 0 to 100 millihenries and the initial voltage of the capacitors could be varied continuously from 0 to 10,000 volts.

For the study of effective shock strengths the operating mode of the experimental defibrillator was selected to simulate a typical clinical unit (10 or 32 microfarads 50 or 100 millihenries 0 to 400 joules stored energy). In this mode of operation the output pulse duration (time between pulse onset and first zero crossing of the underdamped sine wave) which is somewhat dependent upon subject resistance averaged 11 msec.

For the study of toxic shock strengths greater defibrillator capacitance (50 microfarad) charged to higher initial voltages (5,000 to 10,000 volts) was required in order to deliver sufficient energy to produce myocardial damage. In this mode of operation shock durations averaged 14 msec.<sup>1</sup> In both studies, the current waveform

To achieve the highest electrical dose tested, corresponding roughly to the L<sub>10</sub>50 a capacitance of 100 microfarads charged to 10,000 volts was necessary in 11 of 11 animals in one group. With 100 microfarad capacitance the output waveform was an overdamped sine wave as described in reference 10 and in this case the pulse duration is taken as the time required for the pulse to decay to 10 percent of its peak value.

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were similar to those delivered by conventional damped sine wave defibrillators. The delivered pulse durations were within the 2 to 10 msec range described for clinical defibrillators by Finley<sup>14</sup> and within the 4 to 8 msec range we calculated for typical commercially available damped sine wave defibrillators using published values for output circuit components<sup>1</sup> and for the range of human thoracic resistances (25 to 105 ohms) encountered clinically.<sup>15</sup>

**Animal experiments** In the first study reported in detail elsewhere,<sup>1</sup> shocks of a strength near the defibrillation threshold were tested for their efficacy in defibrillating the ventricles of 36 dogs average weight  $14 \pm 7$  kg in which fibrillation was produced by electrical stimulation of the right ventricular endocardium. Transchest ventricular defibrillation threshold was determined in each animal by repeated trials with successive shocks of diminishing peak current amplitude each shock being 10% less than that of the preceding shock. The shocks were administered via 8 cm electrodes in 12 dogs weighing less than 10 kg and via 10 cm electrodes in the larger dogs. The ventricles were never permitted to fibrillate for longer than 30 seconds and another fibrillation defibrillation episode was never conducted until systemic blood pressure had returned to a stable level.

In the second study of damaging and lethal effects a single high intensity damped sine wave shock was given to each of 65 dogs average weight  $8 \pm 2$  kg via 10 cm diameter transchest electrodes. Details of this protocol have been reported previously.<sup>15</sup> In brief each dog was assigned either to a control group which received no shock or to one of six experimental groups which received an unsynchronized shock of approximately 1, 3, 6, 9, 12, 15 or 20 amperes peak current per kilogram body weight (90 to 4700 joules total delivered energy). To calculate the voltage setting required to deliver the desired current the apparent chest impedance to 50 KHz non stimulating sinusoidal current was measured as described by Geddes and associates.<sup>1</sup> Delivered energy was calculated as previously described<sup>1</sup> from current and voltage waveforms registered on a storage oscilloscope. Mean delivered energy doses for the groups of animals ranged from 1 to 512 joules per kilogram

body weight. The hearts were in normal sinus rhythm rather than fibrillation when the unsynchronized shocks were applied to ensure that any observed damage was due to the shock and not to pre-existing circulatory arrest.

Hearts of animals which died immediately after shock as well as hearts of animals which survived and were later killed were removed from the thorax promptly after death. Gross cardiac lesions were observed carefully and were graded according to predetermined criteria.<sup>1</sup> Entire hearts were then fixed in 10% neutral buffered formalin. Blocks of myocardial tissue from 22 standardized sites were collected, embedded in paraffin, sectioned and stained with hematoxylin and eosin. Microscopic lesions were identified and graded according to previously established criteria.

**Determination of efficacy, damage and lethal-ity curves** The criterion for efficacy of transchest shocks was ventricular defibrillation. For each of 36 dogs in the efficacy study five to 20 threshold energy values were obtained and averaged. Histograms were constructed using these mean values to illustrate animal to animal variations in threshold within this population. Percent successful defibrillation vs electrical dose curves were constructed for the 36 dogs according to the method of Goldstein and colleagues,<sup>16</sup> by integrating the threshold energy histograms. Using this technique it was possible in particular to establish the 50% effective dose or ED50 for the population since one half of the dogs had defibrillation thresholds below this value and the other half of the dogs had defibrillation thresholds above this value.

The criterion for toxicity of transchest shocks was any degree of morphologically detectable myocardial damage. According to this criterion a heart was scored as damaged if there were any gross lesions present or if any of the 22 blocks taken for histologic study showed defibrillator induced necrosis of muscle fibers, epicardial reaction or both. In addition the hearts of dogs which died within 15 minutes after shock were scored as damaged although gross and microscopic lesions were often subtle at this early time after injury.

The percentage of animals defibrillated, damaged or killed by shock in each dose group were plotted as functions of the current or energy dose per kilogram body weight. Normalization of dose

one standard deviation

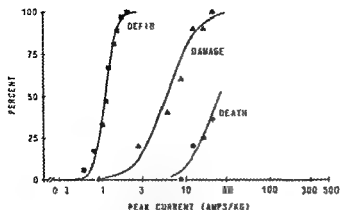


Fig 1 Current dose response curves for defibrillation, morphologic damage and death. The peak current has been normalized to body weight.

by body weight is classically employed in experimental pharmacology and has proved of value in earlier defibrillation studies<sup>14</sup>. For such plots smooth curves were fitted to experimental data by probit transformation and linear regression using the method of Litchfield and Wilcoxon<sup>15</sup> and interpolated values were identified for the ED<sub>50</sub>, TD<sub>50</sub> and LD<sub>50</sub>—the median effective, toxic and lethal electrical doses.

## Results

Fig 1 shows the incidence of defibrillation, morphologic damage and death as functions of delivered peak current in amperes/kg. In terms of peak current the ED<sub>50</sub>, TD<sub>50</sub> and LD<sub>50</sub> were 1.1, 5.8 and 24 amperes/kg, respectively. These values represent the median current doses which were capable of defibrillating, damaging and killing 50% of the animals studied. The corresponding therapeutic indices are TD<sub>50</sub>/ED<sub>50</sub> = 5 for morphologically detectable damage and LD<sub>50</sub>/ED<sub>50</sub> = 22 for death. Thus it took five times as much peak current to produce detectable damage in a typical dog and 22 times as much peak current to kill a typical dog than it did to defibrillate it.

Fig 2 shows the incidences of defibrillation, morphologic damage and death as functions of delivered energy in joules/kg. The ED<sub>50</sub>, TD<sub>50</sub> and LD<sub>50</sub> were 1.7, 30 and 470 joules/kg. The corresponding therapeutic indices were TD<sub>50</sub>/ED<sub>50</sub> = 20 for damage and 11 for death. LD<sub>50</sub> = 320 for death. Hence it took 20 times as much energy to produce detectable damage in a typical dog and 320 times as much energy to kill a typical dog than it did to defibrillate it. Numerical

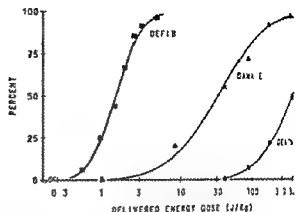


Fig 2 Energy dose response curves for defibrillation, morphologic damage and death. The delivered energy has been normalized to body weight.

dose range and the larger therapeutic indices may be expected when energy is used to describe shock strength because delivered energy varies as the square of the current.<sup>1</sup>

The slopes of the curves of Figs 1 and 2 indicate considerable biologic variability among dogs in their susceptibility to defibrillation, damage or death. Variability in susceptibility to the harmful effects of shock was remarkable. For example, an electrical dose of 120 joules/kg was sufficient to kill 10% of the animals; however, this same dose produced no detectable damage in 12% of the animals while the remaining 78% showed varying degrees of damage. Despite this biologic variability the therapeutic indices were sufficiently large so that there was no overlap between the death and the defibrillation curves and only slight overlap between the morphologic damage and the defibrillation curves. The calculated curves indicate that the risk of detectable damage was 2 to 4% for 90% successful shocks and 5 to 10% for 90% successful shocks. This degree of overlap between the efficacy and toxicity curves is similar regardless of whether current or energy is used to measure the electrical dose.

## Discussion

The studies described in the present paper indicate that therapeutic indices may be calculated for defibrillator shocks on the basis of reasonable criteria for effectiveness and toxicity. The resultant values may be interpreted in a manner analogous to therapeutic indices of drugs. Although similar studies of intentional shock overdose cannot be performed in man, the therapeutic indices of various defibrillating currents

waveforms can be measured in animals in order to design defibrillators with the greatest margin of safety

The relatively large therapeutic indices reported here for animals indicate a reasonable safety margin for damped sine wave defibrillator shocks. Extrapolation of this conclusion to the clinical arena however must be done with caution. The present studies were conducted in healthy animals with normal rather than diseased hearts. Moreover in the efficacy study the time of circulatory arrest due to fibrillation was less than 30 seconds and in the damage study shocks were administered to beating hearts. In general the hearts of animals in both studies were relatively well oxygenated. Human hearts in clinical situations are typically diseased and may be poorly oxygenated at the time of defibrillation. Under these less favorable conditions the therapeutic indices for defibrillation may be significantly different from those reported here.

Nonetheless the available clinical data seem to confirm the relatively low incidence and extent of shock induced damage we have observed at therapeutic shock strengths in dogs. Ehsani and colleagues and Werner and associates have shown 7 and 8% incidence respectively of indirect evidence for damage in humans after high cumulative energy doses from defibrillators. Accordingly in view of both the animal and the human data available at this writing we believe that fear of inducing damage should not be a dominant factor in determining defibrillation dose. Instead effectiveness should be the major criterion.

### Summary

Although prospective studies of defibrillator shock overdose cannot be performed in man the therapeutic indices of various defibrillating current waveforms can be measured in animals. We determined the ratios  $TD_{50}/ED_{50}$  and  $LD_{50}/ED_{50}$  (where  $TD_{50}$  = median toxic or damage inducing dose,  $ED_{50}$  = median effective or defibrillating dose and  $LD_{50}$  = median lethal dose) as measures of the therapeutic index for damped sine wave defibrillator shocks in dogs. Death of an animal and/or any degree of cardiac damage found by gross or microscopic examination were defined as harmful effects of shock analogous to drug toxicity. In terms of peak current the  $ED_{50}$ ,  $TD_{50}$  and  $LD_{50}$  were 1.1, 5.8 and 24 amperes/kg. The therapeutic indices were  $TD_{50}/$

$ED_{50} = 5$  for morphologic damage and  $LD_{50}/ED_{50} = 22$  for death. In terms of delivered energy the  $ED_{50}$ ,  $TD_{50}$  and  $LD_{50}$  were 1.5, 30 and 470 joules/kg. The therapeutic indices were  $TD_{50}/ED_{50} = 20$  for damage and  $LD_{50}/ED_{50} = 320$  for death. These data indicate a reasonable margin of safety for damped sine wave defibrillator shocks in dogs and are consistent with reported incidences of suspected shock induced damage in humans.

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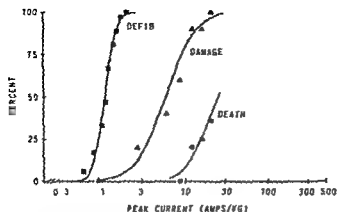


Fig 1 Current dose response curves for defibrillation, morphologic damage and death. The peak current has been normalized to body weight.

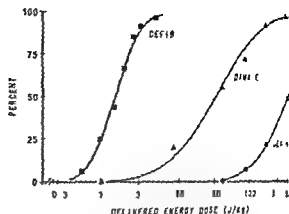


Fig 2 Energy dose response curves for defibrillation, morphologic damage and death. The delivered energy has been normalized to body weight.

by body weight is classically employed in experimental pharmacology and has proved of value in earlier defibrillation studies.<sup>18</sup> For such plots smooth curves were fitted to experimental data by probit transformation and linear regression using the method of Litchfield and Wilcoxon<sup>19</sup> and interpolated values were identified for the ED50, TD50 and LD50—the median effective, toxic and lethal electrical doses.

## Results

Fig 1 shows the incidence of defibrillation, morphologic damage and death as functions of delivered peak current in amperes/kg. In terms of peak current the ED50, TD50 and LD50 were 1.1, 1.8 and 2.4 amperes/kg respectively. These values represent the median current doses which were capable of defibrillating, damaging and killing 50% of the animals studied. The corresponding therapeutic indices are  $TD50/ED50 = 5$  for morphologically detectable damage and  $LD50/ED50 = 22$  for death. Thus it took five times as much peak current to produce detectable damage in a typical dog and 22 times as much peak current to kill a typical dog than it did to defibrillate.

Fig 2 shows the incidences of defibrillation, morphologic damage and death as functions of delivered energy in joules/kg. The ED50, TD50 and LD50 were 1.1, 2.0 and 4.7 joules/kg. The corresponding therapeutic indices were  $TD50/ED50 = 20$  for damage and  $LD50/ED50 = 320$  for death. Hence it took 20 times as much energy to produce detectable damage in a typical dog and 320 times as much energy to kill a typical dog than it did to defibrillate. The

dose range and the larger therapeutic indices may be expected when energy is used to describe shock strength because delivered energy varies as the square of the current.<sup>18</sup>

The slopes of the curves of Figs 1 and 2 indicate considerable biologic variability among dogs in their susceptibility to defibrillation, damage or death. Variability in susceptibility to the harmful effects of shock was remarkable. For example, an electrical dose of 120 joules/kg was sufficient to kill 10% of the animals; however, this same dose produced no detectable damage in 12% of the animals while the remaining 78% showed varying degrees of damage. Despite this biologic variability, the therapeutic indices were sufficiently large so that there was no overlap between the death and the defibrillation curves and only slight overlap between the morphologic damage and the defibrillation curves. The calculated curves indicate that the risk of detectable damage was 0.4% for 90% successful shocks and 5 to 10% for 90% successful shocks. This degree of overlap between the efficacy and toxicity curves is similar regardless of whether current or energy is used to measure the electrical dose.

## Discussion

The studies described in the present paper indicate that therapeutic indices may be calculated for defibrillator shocks on the basis of reasonable criteria for effectiveness and toxicity. The resultant values may be interpreted in a manner analogous to therapeutic indices of drugs. Although similar, studies of intentional shock overdose cannot be performed in man; the therapeutic indices of various defibrillation cur-

# The influence of early repolarization variant on the exercise electrocardiogram: a correlation with coronary arteriograms

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Current criteria for positive and negative treadmill stress tests are based largely on exercise induced S T segment changes in persons with a normal electrocardiogram at rest. A distinctive pattern of S T segment elevation in the resting electrocardiogram of apparently healthy adult subjects referred to in a variety of terms including unusual R T segment deviation, juvenile pattern of adult Negro males, premature repolarization, normal R S T elevation variant, and early repolarization syndrome has been described. Previous investigators have stated that persons with S T segment elevation of the early repolarization variant (ERV) have S T segments return to the isoelectric baseline with physical exercise. The authors concluded that such response to exercise favors a diagnosis of normal variant but no correlations with coronary arteriograms were performed. The purpose of our study is (1) to provide coronary angiography data and treadmill exercise testing correlations in this syndrome of ERV, and (2) to characterize the influence of ERV on the exercise electrocardiogram in a subset of patients with chest pain of possible cardiac origin.

## Materials and methods

During the 90 month period between January 1968 and June 1976 264 patients were referred to the Cardiac Function Laboratory at Grady Memorial Hospital Atlanta Georgia for evaluation of a variety of cardiovascular related problems. All patients underwent both graded treadmill exercise testing and cardiac catheterization studies including selective coronary cineangiography. This subgroup of 264 patients was actually drawn from a much larger population of cardiac patients who did not have both procedures performed. Of these 264 patients were 16 patients seen specifically for evaluation of chest pain syndromes of possible cardiac origin who had resting scalar electrocardiograms characteristic of early repolarization.

The 16 patients consisted of nine black males and seven black females (Table 1). Their ages ranged from 27 to 59 years (mean, 42.4 years).

**Electrocardiograms** All patients included in this study had a minimum S T segment elevation of 0.5 mm above the isoelectric line in at least two standard limb or precordial leads, and in addition in at least one of the four monitored leads at rest (Fig 1). Frank orthogonal X, Y, and Z leads and a bipolar CM lead. The magnitude of S T segment displacement was measured by two of the investigators (B N A and C A G) from the lowest point of the S T segment at least 0.08 sec after the R S T junction (J point) to a baseline constructed by aligning a straight line with successive T P segments. The amount of displacement

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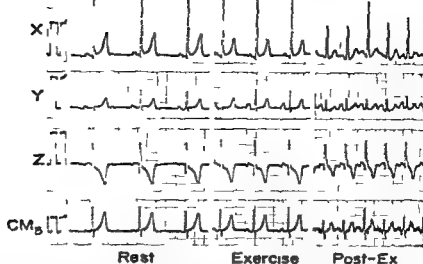


Fig 1A This figure shows the typical response of early repolarization variant (rRV) seen in the left panel (Rest) to be normalized by exercise in one patient. The middle panel shows an early stage of exercise (Exercise) while the right panel (Post Ex) is immediately after exercise has stopped. The ST segment has returned to the isoelectric baseline in the post-ex recording. This is not an abnormal or "ischemic" response to exercise and the coronary angiograms were normal.

Table I Clinical profile

Case no	Age	Sex	Major cardiac problems	Medications
1	27	F	Chest pain rheumatic heart disease with AR and MR	Digitalis sulfadiazine
2	33	M	Chest pain	None
3	33	M	Chest pain essential hypertension	None
4	37	F	Chest pain rheumatic heart disease with AR Mb and MR	Sulfadiazine
5	37	F	Chest pain	Nitroglycerin
6	40	M	Chest pain AR and AS (unknown etiology)	Digitalis thiazide
7	42	F	Chest pain essential hypertension	Nitroglycerin thiazide methyldopa
8	43	F	Chest pain AR (unknown etiology) essential hypertension	Digitalis thiazide
9	43	M	Chest pain suspected MI without objective data	Nitroglycerin thiazide
10	49	M	Chest pain essential hypertension	Methyldopa propranolol nitroglycerin thiazide digitalis
11	51	F	Chest pain essential hypertension	Nitroglycerin propranolol thiazide
12	54	M	Stable angina pectoris essential hypertension	Nitroglycerin thiazide propranolol hydrochlorazine
13	55	M	Chest pain hypercholesterolemia suspected MI without objective data	Nitroglycerin
14	57	M	Stable angina pectoris essential hypertension suspected MI without objective data	Thiazide propranolol nitroglycerin digitalis
15	58	M	Chest pain	Nitroglycerin
16	59	F	Chest pain	Nitroglycerin digitalis

Abbreviations: AR = aortic regurgitation; AS = aortic stenosis; MS = mitral stenosis; MR = mitral regurgitation; MI = myocardial infarction.

was averaged from five successive complexes on the electrocardiogram. The same technique of measurement was utilized in quantitating ST segment changes during exercise. ST segment elevation was determined to the nearest 0.5 mm.

**Exercise protocol.** A modified 10-minute Bruce

exercise protocol was used utilizing a standard commercially available motor-driven belt treadmill with variable speed and variable elevation capabilities. All patients had continuous electrocardiographic monitoring through a Frank orthogonal X-Y-Z and a CM bipolar lead system.

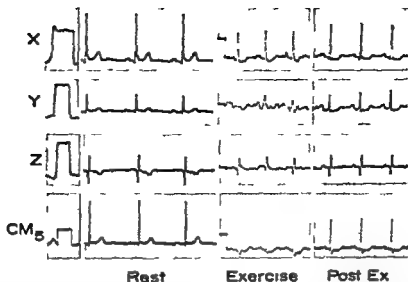


Fig III Another patient's record is seen with progression of the resting ERV (left panel) so that the ST segment is below the isoelectric baseline during exercise (middle panel Exercise). In the right panel (Post Ex) taken 1 to 2 minutes after exercise the ST segments are seen to be 1 mm below the baseline especially in Lead CM5. This abnormal or "ischemic" response occurred in the patient with two-vessel coronary atherosclerotic disease by coronary angiography (patient No. 12).

Each patient became familiar with the exercise procedure by a warm up period (Stage 0) that consisted of walking on the treadmill at a very low energy level (10 mph and 5% grade) for three minutes. Stage 0 was not added to the total duration of exercise score referred to as treadmill exercise duration score (TDS).<sup>11</sup> Each patient then walked for three minutes at each successive stage. Heart rates and blood pressures were recorded at rest before the test during each exercise stage and several times during recovery from exercise. Electrocardiograms of the monitored lead system were also recorded before and during the test and during recovery from exercise. Patient observation was extended for eight minutes following termination of exercise. All patient symptoms were carefully noted. The exercise endpoints from the patients were any of the following: (1) chest pain judged by the physician observer as consistent with myocardial ischemic pain; (2) excessive fatigue; (3) significant decrease in systolic blood pressure sustained during the successive blood pressure determinations; (4) marked ST segment changes; or (5) significant arrhythmia judged as dangerous for the patient. All exercise blood pressure determinations were obtained from a standard sphygmomanometer by the same physician observer during each individual exercise test.

Cardiac catheterization and coronary cinean-

giography. All patients underwent left heart catheterization and standard selective coronary cineangiography using a percutaneous transfemoral approach. Technically high quality left ventriculograms and coronary cineangiograms were obtained with angiographic dye injection. The degree of coronary artery obstruction was expressed as the percentage decrease in artery diameter. In addition the severity of cardiac valvular lesions was assessed in four patients.

### Results

All 16 patients presented with chest pain of possible cardiac origin (Table I). The chest discomfort was defined as angina pectoris in two of the patients who described the discomfort as retrosternal provoked by effort lasting less than 15 to 20 minutes and subsiding in 3 to 5 minutes with rest or the administration of sublingual nitroglycerin. One patient with angina pectoris and two additional patients had been hospitalized for suspected myocardial infarction without diagnostic electrocardiographic and/or enzyme changes of myocardial necrosis. No patient had physical findings of a ventricular aneurysm.

Seven of the patients, six requiring antihypertensive drugs, had well controlled essential arterial hypertension. Four patients had valvular lesions involving the mitral and/or the aortic valve. Because the patients were not entered



Table II

Case no	RS T segment displacement resting ECG														CM
	I	II	III	aV <sub>R</sub>	aV <sub>L</sub>	aV <sub>F</sub>	V <sub>1</sub>	V <sub>2</sub>	V <sub>3</sub>	V <sub>4</sub>	V <sub>5</sub>	V <sub>6</sub>	Y	Z	
1	+	+			+					+	+	+	+		++
2					+			+	+	+		+	+		+
3	++	+			+			+	+	+++	+++	++	+	++	+
4		+	+			+					++	++	+	+	++
5	+						+	++	+	+	+	+	+		++
6									+	++					++
7	+	+			+			+	++	++	+	+	++		+
8	++				+			+	+	+	+	+	++		+
9			+			+			++	+	+	+	++	+	++
10								+	+	+		+	+	+	+
11								++	+	+	+	+	+	+	+
12	+	+			+				+	+	+	+	+		+
13							++	+++	++	+	+	+	+		++
14								+	+	+				+	+
15	+				+			++	++	++	+	+	+		++
16							+	+	+						++

Symbol and abbreviations ECG = electrocardiogram + = 0.5 mm but less than 1.0 mm elevation ++ = 1.2 mm elevation +++ = greater than 0 mm elevation

Table III Summary of responses during TMET

Case no	Peak HR	Peak SBP	DP*	Chest pain	ST segment changes		TDS (minutes)
					Isoelectric	at HR	
1	00	150	30.00	No	Yes	167	61
2	177	200	35.40	No	Yes	136	101
3	180	220	39.60	Yes	Yes	160	103
4	180	145	21.70	No	Yes	150	40
5	187	160	29.92	No	Yes	145	83
6	150	160	24.00	No	Yes	180	80
7	170	200	34.00	No	Yes	175	90
8	177	188	33.28	No	Yes	145	40
9	137	160	21.76	Yes	Yes	120	80
10	167	170	28.39	Yes	No (1.5 mm depression)	158	94
11	143	220	31.46	No	Yes	100	44
12	115	160	18.40	Yes	No (1.0 mm depression)	115	49
13	136	155	21.08	No	Yes	136	81
14	107	125	13.38	Yes	No (1.0 mm depression)	100	60
15	150	200	30.00	No	Yes	125	54
16	100	180	27.00	No	Yes	150	38

Abbreviations HR = heart rate SBP = systolic blood pressure DP = double product (peak HR × peak SBP) TDS = treadmill duration score  
TMET = the double test  
\* divided by 1000

the study in a prospective fashion and because most of the group had other cardiac disorders requiring therapy 14 of the patients were receiving various cardiac medications at the time of exercise testing. These included a thiazide diuretic in nine digoxin in six and propranolol in four.

**ST segment elevation resting electrocardiogram** ST segment elevation was present in 13

patients in Leads V<sub>1</sub>, V<sub>2</sub> and in the Frank orthogonal Lead X in 12 patients in the Frank orthogonal Lead Z in 11 patients in Lead V and in 10 patients in Lead V<sub>6</sub> (Table II). Among the 12 leads ST segment elevation was most prevalent in Lead I (eight patients). No patient had ST segment elevation in lead aV<sub>R</sub>. The mean spatial ST vector was therefore directed to the left inferiorly and anteriorly in the majority of the

Table IV Cardiac catheterization data

Case no	LV contractility	Coronary arteriography	LVEDP (mm Hg)		Ej Fx %	Valvular lesions
			Pre-angio	Post angio		
1	Moderate diffuse hypokinesia	Normal	12	18	51	AR (moderate) MR (trivial)
2	Normal	Normal	10	17	57	None
3	Normal	Normal	17	4	91	None
4	Normal	Normal	16	16	72	AR (moderate) MS (moderate) MR (mild)
5	Normal	Normal	9	13	70	None
6	Mild diffuse hypokinesia	Normal	8	ND	60	AR (severe) MS (mild)
7	Normal	Normal	8	12	67	None
8	Normal	Normal	0	5	88	AR (mild to moderate)
9	Normal	Normal	6	ND	60	None
10	Normal	Normal	-	24	61	None
11	Mild diffuse hypokinesia	Normal	12	11	47	None
12	Normal	75% proximal ALOM	13	21	(post angio = 58)	None
13	Normal	75% proximal LAD	16	10	(post angio = 82)	None
14	Normal	75% proximal LAD	6	ND	76	None
15	Mild diffuse hypokinesia	Normal	17	16	ND	None
16	Normal	Normal	10	78	76	None

Abbreviations: LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; Ej Fx = ejection fraction; LAD = left anterior descending; ALOM = anterolateral oblique marginal; ND = no data; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation.

patients. Six patients (38% of the cases) had no ST segment elevation in the limb leads but all patients with ST segment elevation in the limb leads also had ST segment displacement in the precordial leads.

There was no relationship discernible between the patient's major and cardiovascular disorders, medications, and the degree and distribution of ST segment elevation in his resting electrocardiograms.

**Correlation of treadmill exercise responses with cardiac catheterization and coronary angiographic data.** A summary of the pertinent treadmill exercise data is presented in Table III. Six of the 16 patients attained a treadmill exercise duration score (TDS) of 85% or greater of predicted average TDS for normal sedentary subjects; four achieved a TDS of 60% to 84% and the remaining six of the 16 patients had a TDS of 43% to 59% values for average exercise heart rates for age and sex matched sedentary normal subjects were drawn from the author's (C. A. G.) own exercise laboratory data.

None of the 16 patients had his resting ST segment elevation increase with exercise. In 13 patients (81%) the elevated ST segments

returned to the isoelectric baseline (normal sized) during exercise with heart rates between 100 and 167 beats per minute (mean 139 beats per minute). All 13 of these patients had normal coronary arteriograms (Table IV) and none had angiographic evidence of a left ventricular aneurysm. Three of these 13 patients had mild to moderate diffuse left ventricular hypokinesia but with normal coronary arteries (Table IV). In two patients (Nos. 1 and 6) the left ventricular dysfunction was probably due to moderate to severe chronic aortic regurgitation, whereas in the third (No. 15) it was unexplained. The remaining three (Nos. 10, 12, and 14) of the 16 patients developed significant ST segment depression (10 to 15 mm) at an exercise heart rate of 158, 115, and 100 beats per minute, respectively. Of these three patients, two (Nos. 12 and 14) had significant coronary atherosclerotic occlusive lesions (Table IV) whereas the third (No. 10) had normal coronary arteries and normal left ventricular contractility but moderately increased left ventricular end-diastolic pressures. This latter patient had hypertensive cardiovascular disease and a history of chronic alcohol abuse.

Chest pain experienced during exercise did not

permit separation of patients with significant coronary atherosclerotic disease from the rest of the study group with normal coronary anatomy (Tables III and IV)

Rare premature supraventricular and unifocal premature ventricular complexes not previously present in the resting electrocardiograms were observed during exercise in patients No 1 and No 10 and in patient No 13 respectively No other arrhythmias were noted during or following exercise in the 13 other patients in our study

### Discussion

Typically the S T segment of the early repolarization variant (ERV) is characterized by an upward concave elevation of the R S T segment that arises from the descending limb of the R wave in a smooth curve without forming a sharp angle with that R wave (Fig 1) The S T segment merges with the ascending limb of a usually tall positive and peaked T wave In addition a definite notch or slur on the downstroke of the R wave and/or a distinct J wave are frequently present

In our patients and those reported by others, the characteristic S T segment elevation was most prominent and most frequently observed in the standard limb Lead I and in the midprecordial Leads (V<sub>4</sub> and V<sub>5</sub>) and no patient had the S T elevation limited to limb leads alone In the majority of instances S T displacement did not exceed 2 mm However Goldman reported 23 predominantly young healthy adults whose electrocardiograms had shown S T elevations of 2 to 4 mm in the mid and left precordial Leads (V<sub>4</sub> through V<sub>6</sub>)

Although the ERV has been encountered in patients with a variety of cardiac disorders, including rheumatic valvular and coronary atherosclerotic heart disease, this electrocardiographic finding is not an objective marker of cardiac disease The ERV is seen in approximately 25% to 61% of apparently healthy adults Although it has been observed in either Black or Caucasian individuals, some studies report a higher prevalence of the ERV in young adult Black males

The precise electrophysiologic genesis of the S T segment elevation is unknown Several possible explanations previously proposed include (1) hyperapoptonia (2) ischemia and early repolarization in the myocardium occurring before depolarization (3) whole myocardium

The benign nature of the ERV has been established by longitudinal follow up in individuals with this electrocardiographic In a recent review of the electrocardiogram patients with the ERV syndrome Kamber Phillips found persistence of this pattern many years and a general tendency to decrease S T segment displacement with increased age 26% of their 65 patients the S T elevation appeared in at least one follow up electrocardiogram, while in the 48 other patients elevation was discernible in every recording Furthermore, the degree of S T displacement greatly from one electrocardiogram to another the individual patient Others have reported that individuals with the ERV with S T elevation at rest have S T segments return to isoelectric baseline (normalize) with physical exercise, and concluded that such response is a diagnosis of normal variant and no heart disease—but no correlations with coronary arteriograms were performed

Our study provides correlates between responses to treadmill exercise testing and coronary cineangiography in patients with ERV verifies the benign nature of this finding in a subset of patients with chest pain of possible myocardial origin and S T segment elevation suggestive of ERV in the resting electrocardiogram all except one patient (No 10 with normal coronary arteriograms) had the S T segment return to the isoelectric baseline with treadmill exercise Thus patient (No 10) without evidence of coronary atherosclerotic disease but with moderate left ventricular dysfunction of unknown cause developed significant S T depression (1 mm below isoelectric baseline) during treadmill exercise Two patients (Nos 12 and 14) with significant coronary atherosclerotic disease developed similar ischemic S T segment depression with exercise Thus while ERV at rest may be normalized by graded physical exercise in the absence of significant coronary atherosclerosis the presence of ERV does not prevent the usual electrocardiographic manifestations of exercise induced myocardial ischemia

The influence of propranolol and digitalis on the response of the ERV to physical exercise is unknown Several studies report that propranolol may prevent the appearance of ischemic electrocardiographic changes even when exercise is continued to the onset of myocardial ischemic pain and may change a positive exercise test to a

negative result. These observations, however, did not involve patients with the ERV. The influence of propranolol on the response of the ERV to exercise stress testing remains speculative. Interestingly, in our series, only the two patients with significant coronary atherosclerotic disease and positive ischemic S-T segment depression provoked with exercise were receiving propranolol at the time of treadmill testing. Digitalis on the other hand can elicit a false positive ischemic exercise electrocardiographic response in persons without myocardial ischemia. In our patients with the ERV, however, digitalis did not appear to produce false positive ischemic S-T segment changes during exercise.

### Summary

Sixteen adult patients with S-T segment elevation in their resting electrocardiograms characteristic of early repolarization variant (ERV) and chest pain syndromes of possible myocardial ischemia were evaluated with both treadmill exercise electrocardiography and coronary arteriography. Of 14 patients with normal coronary arteriograms, 13 had their resting S-T elevation return (normalize) to the isoelectric baseline with physical exercise, while one patient with normal arteriograms and normal left ventricular contractility but moderately elevated left ventricular end diastolic pressure of unknown etiology developed significant S-T depression with exercise. Two patients with significant coronary atherosclerotic occlusive lesions developed ischemic S-T depression during treadmill testing. Symptoms developed during treadmill exercise did not distinguish patients with coronary artery disease from those without. Thus, while ERV at rest may be normalized by graded physical exercise in the absence of significant coronary atherosclerosis, the presence of ERV does not prevent the usual electrocardiographic manifestations of exercise-induced myocardial ischemia.

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# Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement

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The antithrombotic effects of drugs that modify platelet functions have been evaluated in several clinical trials<sup>1-3</sup>. Such agents may be particularly useful in conditions related to arterial thrombosis because platelets play a dominant role in the formation of the thrombus.<sup>4</sup> Platelet adhesion, release, and aggregation are important steps in the thrombotic process.<sup>5</sup> Several drugs inhibit the platelet release reaction and thereby the subsequent irreversible aggregation.<sup>6</sup> Most important are acetylsalicylic acid (ASA), indomethacin, sulfinpyrazone, and butazolidin, while dipyridamol may reduce platelet aggregation through other mechanisms.<sup>7</sup> ASA is most extensively used, and the results from several studies indicate a preventive effect on arterial thrombus formation.

Anticoagulant in adequate doses effectively prevents venous thromboembolism because plasma coagulation is the predominant mechanism in this type of thrombosis. Low dose heparin administration has recently been introduced as an alternative treatment in this condition.<sup>8</sup> Anticoagulant drugs are also widely used in the prevention of arterial thrombosis, particularly after prosthetic valve implantation, and are employed by several centers in coronary heart disease. The effect is limited, however, and further

research is needed to find a therapy that effectively inhibits arterial thrombus formation. The combination of drugs that modify platelet function and anticoagulants may prove useful since it attacks more than one step in the thrombotic process.<sup>9</sup> A combination of anticoagulants with dipyridamol<sup>2</sup> and later with ASA<sup>10</sup> gave an antithrombotic effect superior to anticoagulants alone in patients with prosthetic heart valves. Others have combined two drugs that affect platelet function.<sup>11</sup>

All agents that inhibit thrombus formation are potential inducers of bleeding since the mechanisms responsible for stopping hemorrhage are the same that form thrombi when stimulated pathologically.<sup>12</sup> Combined antithrombotic therapy might be particularly dangerous since it affects more than one part of the hemostatic mechanism. Therefore the tendency of bleeding that a therapy may induce should always be evaluated along with its antithrombotic effects.

Patients with prosthetic heart valves are particularly useful for studies on prevention of arterial thromboembolism because such complications are frequent and quite well defined.<sup>13</sup> In such patients, however, the platelet adhesiveness is reduced,<sup>14</sup> the bleeding time is prolonged,<sup>15</sup> and platelet survival is shortened,<sup>16</sup> most probably because of trauma inflicted by the prosthetic valves.<sup>17</sup> This reduced platelet reactivity might in itself predispose to bleeding.

Patients with aortic ball valve prostheses have participated in a randomized clinical trial and have received either anticoagulants alone or com-

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combined with ASA.\* In the present study the bleeding complications are analyzed in relation to platelet function, intensity of anticoagulant treatment and administration of ASA.

#### Materials and methods

**Patient material** Included in the study were 148 patients who had received a Starr Edwards aortic ball valve more than two years previously and who were willing to participate. Two types of the valve had been used: series 1200 with silicone rubber ball and metal cage and series 2300 with hollow Stellite ball and cloth covered cage. Twenty-one patients had been excluded either because they were older than 70 years had suffered gastrointestinal or other types of bleeding previously or because other heart operations were planned. They had all taken anticoagulants since the operation.

**Antithrombotic study** The patients received either one gm of microencapsulated ASA (Colfarit Bayer AG Wuppertal West Germany) daily or placebo according to randomization; the study being double blind. The patients were strictly informed not to take any other preparations containing ASA, a list with all forbidden preparations being given to them. All patients received anticoagulant therapy, the intensity of which was controlled by Thrombotest (TT)<sup>22</sup> aiming at levels of 10% of normal activity.

We had decided that ASA or placebo should be discontinued after all acute complications except those related to thromboembolism or cardiocirculatory performance. This was done in order to avoid possible undesired effects of the combined therapy.

The patients were examined after one and finally after two years. A clinical examination was done, x-ray of the heart and lungs was performed and an ECG and several routine blood tests were taken. Three stool specimens from each patient were examined for occult blood by the benzidine method and plasma salicylate levels were determined. The few patients that were unable to meet were controlled by local physicians or hospitals and questionnaires were sent to the doctors of all patients in order to obtain complete information.

The diagnostic criteria used for thromboembolic complications and a more detailed description of the management of the study have been published earlier.<sup>2</sup>

**Table 1** Bleeding complications in patients receiving ASA and anticoagulants and in patients on anticoagulants alone

Type of bleeding	Patients treated with			
	ASA and anticoagulants		Placebo and anticoagulants	
	Episodes	Deaths	Episodes	Deaths
Intracranial	2	1	3	2
Gastrointestinal	11		2	
Other	■		1	
Total	15	1	6	■

**Platelet functions** Platelet counts, platelet retention in glass bead columns and bleeding time were determined in 16 patients with bleeding complications either before the study started or after discontinuation of ASA or placebo when the patients had recovered completely from the effects of blood loss. The results were compared with those from unselected patients without bleeding complications. All patients received anticoagulants when tested.

Platelets were counted in a hemocytometer using a modification of Nygaard's method.<sup>1</sup> Platelet adhesiveness was estimated from retention in glass bead columns according to the modified method of Hellem.<sup>2</sup> The bleeding time was measured from two incisions by a modification of Ivy's method.<sup>3</sup> The length of the cuts was approximately one cm and the depth adjusted so that a drop of a matchhead's size emerged in 30 seconds.

#### Results

The combined therapy was given to 75 patients while 73 received placebo and anticoagulants.

Bleeding complications were more frequent in patients on ASA and anticoagulants than in those on anticoagulants alone (Table 1). The incidence being 139 and 47 episodes per 100 patients per year respectively. The difference is statistically significant ( $p < 0.02$ ). The difference is entirely due to the significantly higher incidence of gastrointestinal hemorrhage ( $p = 0.01$ ) in the former group of patients. Intracranial bleeding which was the most serious complication was not more frequent in patients who received ASA in addition to anticoagulants. It

**Table II** Bleeding complications classified according to the effect on whole blood hemoglobin (hb) concentration (intracranial hemorrhage is not included)

Lowest hb concentration	Patients treated with	
	ASA and anticoagulants	Placebo and anticoagulants
Lower than 8 g/dl	5	2
8 to 11 g/dl	6	
Higher than 11 g/dl	2	1

**Table III** TT values before bleeding episodes in the two groups of patients with aortic ball valve prostheses

TT of normal	Patients treated with	
	ASA and anticoagulants	Placebo and anticoagulants
Lower than 5	4	2
6 to 10	8	4
11 to 15	1	
16 to 20	1	

**Table IV** Relation between the intensity of anticoagulant therapy and the severity of bleeding (intracranial hemorrhage is not included)

TT before bleeding	No of patients with hb concentration		
	>11 g/dl	8-11 g/dl	<8 g/dl
Lower than 10"			4
10" to 15"	2	5	3
15" to 20"		1	
20" to 30"	1		

caused one death in patients on combined therapy and two in the placebo group

The patient taking ASA had for some weeks clinical signs of sepsis before she died from intracranial hemorrhage and autopsy revealed that the bleeding had occurred in a septic focus. In a second patient on combined therapy and subdural hematoma developed less than one week after the start of the study but this 76 year old woman recovered completely after operation.

In the placebo group a 53 year old man died after two days in deep coma. A autopsy a subdural hematoma as well as an embolus in the middle cerebral artery was found. There was

**Table V** Time relationship between the start of the study and the onset of bleeding

Time from start of therapy until bleeding	Patients treated with	
	ASA and anticoagulants	Placebo and anticoagulants
Less than 1 week	3	
1 week to 1 month	4	
2 to 6 months	2	1
7 to 12 months	4	2
13 to 18 months		1
19 to 24 months	2	1

however no connection between bleeding and embolus and no history of trauma could be revealed. It was regarded most likely that the bleeding had occurred first and was of the greatest significance. Two other men on anticoagulants alone suffered from intracranial hemorrhage, one died the other survived after surgical evacuation but with considerable functional disturbances. The blood pressure was normal in all patients with intracranial bleeding.

The severity of the other types of bleeding episodes was estimated from the lowest hemoglobin concentration after the hemorrhage (Table II). In five patients on combined therapy and two on anticoagulants alone Hb fell below 8 g/dl and blood transfusions were required. The blood loss was gastrointestinal in these seven patients and all of them recovered completely.

Only two of the bleeding episodes in the group receiving combined therapy occurred after TT values higher than 10% (Table III). The TT values of all patients throughout the observation period were reflected by those found at the annual controls. In comparison only 33% of all values in patients on combined therapy and 28% in those on anticoagulants alone were 10% or lower. The differences between the proportions of low TT values before bleeding and at annual controls were highly significant in both groups of patients ( $p < 0.01$ ). The episodes of intracranial bleeding all occurred at TT values of 9% or lower. Thus intense anticoagulant therapy was associated with an increased risk of bleeding particularly when ASA was given.

The severity of the bleeding episodes was related to the intensity of the anticoagulant therapy before hemorrhage (Table IV). The results indicate that the blood loss at low TT

Table VI Comparison of platelet functions in patients with and without bleeding episodes with level of significance

	Patients with bleeding			Patients without bleeding			p
	No	Mean	S.E.M	No	Mean	S.E.M	
Platelet per $\mu$ l	19	1.6 400	13 900	133	191 300	5 000	N.S
Adhesiveness, %	16	24.3	2.3	67	35.4	2.5	p < 0.05
Bleeding time min	16	6.9	0.5	24	6.7	0.4	N.S

values regardless of ASA ingestion tended to be particularly abundant. Thus Hb fell below 8 g/dl during all episodes in patients with TT at 5% or lower and two of the five episodes of intracranial bleeding occurred at such low TT values.

The time from the start of the study until the onset of bleeding was recorded (Table V). Nearly half of the episodes developed during the first month of ASA ingestion and only two patients on combined therapy bled during the second year of the study. In the placebo group however the six episodes were scattered throughout the observation period and could be expected since the patients had received anticoagulants constantly since the operation.

Platelet counts were moderately but insignificantly lower in the patients who developed bleeding episodes than in the others and the bleeding time did not differ significantly between the groups (Table VI). Platelet retention in glass bead columns which is considerably reduced in patients with prosthetic ball valves was significantly lower ( $p < 0.05$ ) in patients with bleeding episodes than in those without.

Occult blood loss was detected in 12 of the 47 patients who remained on combined therapy until the end of the study, and in three of the 53 patients of the placebo group.

## Discussion

The study revealed a higher incidence of bleeding episodes in the ball valve patients who received ASA in addition to anticoagulants than in those given equally intensive anticoagulant therapy alone. The rate of complications was however acceptable in view of the effective protection achieved against arterial thromboembolism with the combined treatment. Moreover the higher incidence was entirely attributable to gastrointestinal bleeding from which all recovered.

Bleeding complications are not rare in patients who receive anticoagulants after valve replacement and intracranial hemorrhage which is particularly serious, did not occur more frequently in our study than in others.<sup>2-4</sup> A comparable antithrombotic effect was demonstrated in a simultaneously performed study on valve patients as in our trial<sup>10</sup> while the incidence of bleeding was similar in these two groups and slightly lower than in our patients given combined therapy. The daily dose of ASA was 0.5 gm and the anticoagulation aimed at TT values of 8 to 15% but the intensity was not further documented. The combination of dipyridamole and anticoagulants offered a good antithrombotic effect in a previous trial in ball valve patients but lethal intracranial bleeding occurred in two of 79 patients in one year while gastrointestinal hemorrhage did not occur.<sup>2</sup>

The thrombotic and hemostatic mechanism and the interactions between platelets and anticoagulation are complex.<sup>1</sup> Thus platelet phospholipoproteins exposed by the platelet release reaction accelerate the intrinsic coagulation system with the formation of thrombin which is a potent inducer of just the platelet release reaction. ASA and anticoagulants affect thrombosis and thereby hemostasis on different levels. ASA inhibits irreversible platelet aggregation by inhibiting the enzyme cyclo-oxygenase preventing the production of labile endoperoxides which are strong inducers of the release reaction.<sup>11</sup> Anticoagulants lead to a diminished production of some coagulation factors and thereby to reduced thrombin formation after activation of coagulation. One could therefore expect an additive or even synergistic effect on arterial thrombosis and hemostasis by these drugs. The reduced adhesiveness of the platelets a reactivity involved in primary hemostasis might further potentiate the inhibitory effect on thrombosis and hemostasis.



Consequently a particularly high incidence of bleeding complications could be feared in patients given combined therapy, since hemostasis would be affected in three different ways.

The prevention of arterial thromboembolism must be weighed against the increased risk of bleeding and our study represents a step in the search for a therapy that may offer a satisfactory protection against arterial thrombosis at an acceptable risk of bleeding. Whether this can be achieved by intensive anticoagulant therapy or by large doses of ASA or by a combination of the two in more conventional doses, can only be determined in clinical trials.

The influence of each of the two drugs of the reduced platelet reactivity may to some extent be derived from our results. Thus the dose of ASA undoubtedly increased the bleeding tendency but apparently only from the gastrointestinal tract. Such bleeding is also well known to occur after ASA ingestion even in patients without anticoagulants and with a presumably normal platelet function. This indicates that local irritation of the mucosa either from the normal gastric content or from ASA liberated in spite of the mucosal protection is important in addition to the general effect on hemostasis. Bleeding may be more easily precipitated in some patients than in others because their platelets might be particularly sensitive to the effects of ASA.

The role of anticoagulants for the occurrence of bleeding complications also seems obvious. Thus, bleeding correlated with the intensity of the therapy as judged from the TT levels before the episodes. And equally important the severity of bleeding was related to the intensity of the treatment. Intensive anticoagulation was therefore without doubt responsible for several serious bleeding episodes. In a study on the effects of intensive anticoagulant therapy in coronary heart disease a condition with near normal platelet function bleeding episodes occurred almost as frequently as in our patients using combined therapy. The majority of TT values were below 10% with a mean of 8% as compared to 11% in our trial. In studies with less intensive anticoagulation bleeding is less frequent. Standardization of reagents for control of anticoagulant therapy is difficult, and different thromboplastins give different results. The coagulation activity in percent of normal as measured with Thrombotest and Simplastin A roughly parallel each other

while most other methods give considerably higher values. Our results demonstrate the intensity of anticoagulant therapy is also important for the bleeding tendency when given in combination with ASA.

The role of the reduced platelet function is more difficult to evaluate. However the correlation between the number of adhesive platelets and the bleeding time as well as the particularly marked prolongation when ASA is given to patients with a low platelet adhesiveness, suggest that the reduced platelet reactivity was of importance. The low number of adhesive platelets in patients who developed bleeding as compared to the others indicate that reduced platelet adhesiveness predisposed to hemorrhage. The considerably reduced platelet adhesiveness is not further diminished by ASA ingestion which demonstrates that the trauma by the valve and ASA influence different platelet functions.

Bleeding tended to occur shortly after the start of ASA administration which may have two possible explanations: the bleeding may be initiated as soon as the TT level drops according to unavoidable physiological variations, or some patients may be particularly susceptible to the effect of ASA. A combination of the two mechanisms is probably the most likely cause of early gastrointestinal bleeding at low TT values. The results indicate that the combined therapy can be continued more safely if it is tolerated for the first two months.

In conclusion the greater tendency towards gastrointestinal bleeding was acceptable in relation to the antithrombotic effect achieved with the combined therapy. The correlation between the intensity of anticoagulation and the incidence of bleeding raises a question which is the issue of a present investigation. Will a slightly less intensive anticoagulant therapy in combination with ASA offer an equally effective protection against arterial thromboembolism and will the bleeding tendency thereby be reduced?

### Summary

Bleeding complications were evaluated in 14 patients with single Starr Edwards aortic ball valve prostheses in a study designed to prevent arterial thromboembolism. They received either one gm of ASA daily or placebo in combination with anticoagulants and were observed for 1 1/2 years. Only two embolic episodes occurred in

- patients on combined therapy as compared to 12 episodes in the placebo group
- Fifteen bleeding complications developed in patients receiving ASA seven during the first month. Two patients suffered intracranial hemorrhage and one died; the others recovered completely. Six episodes occurred in patients on anti-coagulants alone; three intracranial complications caused two deaths. The higher incidence of bleeding induced by the combined therapy was entirely due to gastrointestinal hemorrhage indicating that irritation of mucosa was important in addition to the ASA induced inhibition of hemostasis.

The intensity of anticoagulation correlated significantly with the occurrence of bleeding and severe blood loss developed only after intensive therapy. This raises the question whether a slightly less intensive anticoagulation in combination with ASA will maintain a satisfactory antithrombotic effect at a lowered risk of bleeding.

Platelet adhesiveness, which is partly responsible for primary hemostasis, was reduced in the ball valve patients and more in those who bled than in the others.

It is concluded that the higher incidence of gastrointestinal bleeding in patients who received ASA and anticoagulants than in those on anti-coagulants alone was acceptable when compared to the antithrombotic effect achieved with the combined treatment.

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## - Excitation of ischemic myocardium altered properties of conduction refractoriness and excitability

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Conduction delays within the ischemic subepicardium have repeatedly been implicated in the genesis of ventricular arrhythmias in acute 'subacute and chronic' myocardial infarction. In the first few minutes after coronary artery ligation the heterogeneous nature of the electrophysiological properties of the ischemic zone have been noted and closely correlated with the onset of ventricular arrhythmias.<sup>1-4</sup> However because conduction and refractoriness change rapidly during this phase and because of the frequent interposition of lethal ventricular arrhythmias the ability to study the electrophysiology of acutely ischemic myocardium is limited. A recent study by Elharrar and associates involved ventricular pacing in acute myocardial ischemia utilizing a pacemaker which determined diastolic threshold every 45 seconds. These workers measured a gradient of excitability threshold between normal and ischemic myocardium within the first minutes of ischemia.

We have previously reported that dogs with subacute myocardial infarction provide a more stable model for analysis of the association between epicardial conduction disturbances and

ventricular arrhythmias.<sup>5-7</sup> Employing this model we detected altered properties of conduction refractoriness and excitability of ventricular epicardium overlying the infarct zone in the period 3 to 10 days after myocardial infarction. The relationship between these altered electrophysiological properties and induced rate-dependent myocardial arrhythmias was examined in the intact animal as well as at a cellular level. This study set out to examine the mechanisms whereby such arrhythmias traverse the abnormal epicardium overlying the infarction zone and eventually reenter the normal myocardium.

### Materials and methods

Experiments were performed on 18 adult mongrel dogs weighing 10 to 30 kg and anesthetized with intravenous sodium pentobarbital (30 mg/kg). A Harvard respirator provided mechanical ventilation of the lungs with room air through a cuffed endotracheal tube. A left thoracotomy in the fourth intercostal space was performed. The pericardium was incised and the anterior descending coronary artery was exposed immediately below the origin of the anterior septal branch. A silk ligature was placed around the artery and the vessel was occluded. In all 18 dogs including three sham operated dogs (not subjected to coronary artery ligation) the epicardium was repaired and the thoracotomy was closed. Three to nine days later each animal underwent repeat thoracotomy using the same anesthetic and ventilatory procedures described above. The pericardium was reopened. The area of myocardial infarction was visually identified. Three to five pairs of fine

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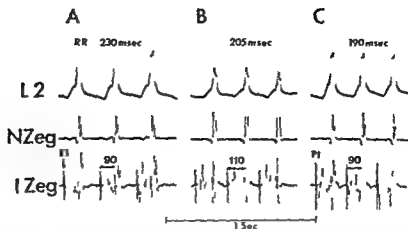
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**Fig 2** The effect of increasing heart rate and stimulus strength on epicardial conduction and QRS morphology in the infarcted dog heart. Abbreviations are the same as in Fig 1. Pacing is from the IZ at an RR cycle length of 230 msec. Note the fractionated activity preceding the QRS and coincident with the direction of the delta wave in the ECG. The interval from the onset of the PI to the major deflection of the IZeg = 90 msec. In panel B at a faster rate (RR of 205 msec) the PI to IZeg increases to 110 msec. Concurrently, the QRS morphology is altered. In panel C by increasing the stimulus strength of the pacer from 8 to 5 volts the conduction time from the PI to the IZeg is reduced to 90 msec, and the QRS reverts to the morphology seen at the slower rate, although the heart rate has actually been increased (RR = 190 msec).

During the procedure areas of maximum activation delay were sought within the subepicardium overlying the infarcted area. This was achieved by varying the position of the bipolar wire electrodes within the subepicardium of the infarct zone. In all experiments ventricular pacing from the superficial subepicardium was carried out from at least three (and as many as five) areas overlying the infarct zone. The pacing techniques employed were the same as those used to pace from the normal myocardium. Attempts to pace from within the myocardium or deep subepicardium of the infarcted zones were invariably unsuccessful with plunge wire electrodes even at stimulus intensity as high as 150 volts and 10 to 20 msec duration. Care had to be taken to place the plunge wire electrodes in the most superficial subepicardium in order to achieve ventricular pacing. If during the various pacing procedures ventricular fibrillation occurred no attempt at resuscitation was made.

## Results

In dogs with subacute myocardial infarction ventricular pacing from normal myocardium was associated with regular capture and constant QRS morphology at rates as fast as 360 beats/minute. Moreover the stimulus to QRS interval 15 to 20 msec was constant at all heart rates up to 360/minute. In this report we directed our

attention to the electrophysiological abnormalities in response to pacing stimuli delivered to the subepicardium overlying the infarction.

When pacing the ventricle from the epicardium basic differences in activation were noted according to the site of stimulation in relation to normal or infarcted myocardium. Fig 1 panel A illustrates electrograms (eg) from the normal zone (NZ) and from subepicardium overlying the infarct zone (IZ) together with electrocardiogram Lead 2 (L2). There is delay of conduction within the subepicardium overlying the IZ which manifests as fractionated and prolonged activation recorded by the IZeg. Ventricular pacing from a site in the NZ (panel B) at the same rate (RR = 215 msec) is associated with little change in either NZeg or IZeg recordings. Total activation time as measured from the IZeg is 125 msec. In panel C pacing at the same rate from a subepicardial site close to the IZeg demonstrates early activation of the neighboring IZeg (lower trace). The QRS and NZeg are activated after a prolonged exit time from the IZ. Total activation time is now 170 msec. A "delta" wave appearance of the initial QRS upstroke is seen in the electrocardiogram. The QRS was regularly deformed in this manner when pacing from the subepicardium overlying the infarction presumably due to delayed conduction with relatively slow spread of activation through this abnormal muscle. When

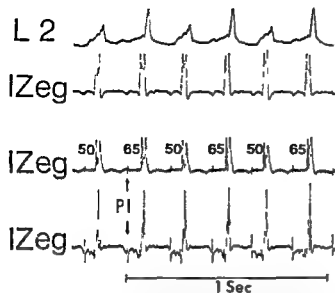


Fig 3 The effect of IZ pacing at a constant rate and stimulus strength on QRS morphology and IZ conduction. Pacing from a particular site in the abnormal epicardium overlying the infarct in this experiment showed an alternating QRS morphology in the ECG coincident with an alternating conduction time from the pacer impulse (PI) to the various electrograms recorded in other portions of the abnormal epicardium (three traces labeled IZeg)

the impulse exits into the normal zone and conducts via normal pathways the remainder of the QRS is not inordinately delayed.

For a given site of stimulation in the abnormal zone the time required for an impulse to exit from that abnormal zone and the pattern of ventricular activation depended on the rate and strength of stimulation. In Fig 2 ventricular pacing (RR = 230 msec - stimulus 8 volts) from the abnormal subepicardium is associated with prolonged conduction in this area. The interval between stimulus and R wave (and normal zone activity) is approximately 90 msec. Increasing the stimulus rate (RR = 205 msec) results in further conduction delay in the subepicardium overlying the infarction (110 msec) and an obvious change in QRS morphology. Stimulus strength in panel C has been increased to 25 volts and the conduction time within the abnormal zone and QRS configuration have reverted to values shown in panel A. This has occurred in spite of a further increase in pacing rate (RR = 190 msec). In all animals studied ventricular pacing from one or more abnormal zone sites resulted in changes of QRS morphology dependent upon rate and strength of stimulation.

Fig 4 illustrates alternation of conduction

the subepicardium overlying the infarction. Stimulus strength (8 volts) and rate are constant. This pacing rate (RR = 210 msec) is associated with alternation of QRS patterns and of conduction time from stimulus to all ventricular electrograms but the measured values (msec) are shown for the lower IZeg only. This phenomenon of alternation of QRS morphology and/or infarct zone conduction time was seen in 24% of our experiments over a narrow range of pacing rates. These rates varied from one animal to another and also depended upon the strength of the stimulus.

When pacing from the normal ventricular subepicardium conduction delay within the abnormal zone was observed but complete entrance block to any particular IZ site was never seen. In contrast pacing from the subepicardium of the infarct zone resulted in block to the normal zone and failure to capture the ventricle. Fig 4 is from the same experiment as is illustrated in Fig 3. However the pacing stimulus strength is reduced (6 volts) and the rate is faster (RR = 190 msec). Conduction time from the stimulus to the IZ electrogram has increased to 75 msec. At the same pacing rate but with stimulus strength reduced to 4.5 volts panel B demonstrates failure to achieve capture with alternate stimuli. In this instance as in others it was not possible to determine if these observations were due to failure of excitation by alternate stimuli or to exit block from the subepicardium over the infarct zone surrounding the pacing bipole. It may also be noted that when ventricular capture occurs there is a change in QRS configuration and improvement in abnormal zone conduction (55 msec) presumably due to the relative slowing of the heart rate.

Figs 5 and 6 indicate some of the varied ways in which during ventricular pacing from the subepicardium overlying the infarction (with constant stimulus strength and rate) spontaneous failure of pacing was observed. In Fig 5 in panel A electrocardiogram Lead 2 (L2) and one infarct zone electrogram (IZeg) are shown. The panel illustrates a sequence of Wenckebach conduction delay from the stimulus to the electrogram in the abnormal subepicardium and ultimate failure of capture by the pacing stimulus. Prolongation of conduction time between stimulus and onset of abnormal zone activation (in this particular site) gradually increases from 10 to 32 msec before block occurs. In panel B at a relatively slow

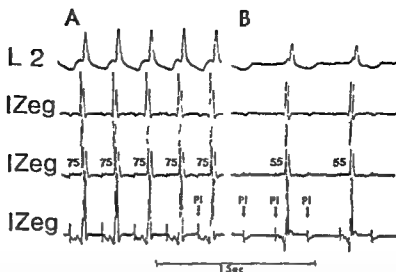


Fig 4 The effect of pacing from the abnormal epicardium at rapid heart rates on QRS morphology and conduction in the IZ. This figure is a continuation of the traces shown in Fig 3. In panel A the stimulus strength has been reduced to 6 volts and the heart rate increased to a cycle length of 190 msec. Note that the conduction from the pacer impulse (PI) to the onset of the middle electrogram remains constant at 75 msec. In panel B the stimulus strength was further reduced to 4.5 volts resulting in a 1 relation ship between pacer impulses and ventricular activation. In every alternate beat the conduction time from the pacer impulse to the IZeg is 55 msec and the QRS morphology is different from that seen in panel A. See text for further discussion.



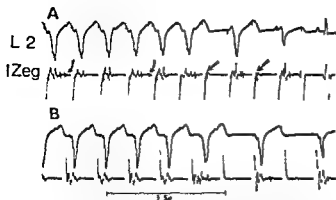
Fig 5 Two forms of activation failure seen during pacing from the abnormal epicardium in the infarcted dog heart. In those panels ECG (L2) and an electrogram from the abnormal epicardium (IZeg) are shown. In panel A ventricular pacing initiated at a constant rate after the first sinus beat shows progressive increase in the conduction time from the pacer impulse to the onset of the QRS complex as well as a similar delay in the interval between the pacer impulse and the onset of the IZeg. When the delay reaches a maximum of 32 msec block is seen in the next beat with subsequent occurrence of 2:1 ventricular activation. Note the change in QRS morphology between the 1:1 and 2:1 sequences. In panel B at a constant pacing rate (RR = 390 msec) there is a sudden loss of excitation after the fifth paced impulse. However this is not preceded by any measurable change in the interval between the pacer impulse and onset of the QRS or the IZeg. See text for details.

heart rate (RR = 390 msec) the fifth and subsequent stimuli (S) abruptly fail to achieve ventricular capture. Preceding infarct zone electrograms are stable. The initial stimulus which fails to capture is well beyond the T wave of the previous

beat. This example of apparent sudden excitation failure may also be a result of prolonged (post repolarization) refractoriness (also see Fig 7).

In Fig 6 panel A at a constant pacing rate the pacing impulse (PI) abruptly fails to capture the





**Fig 6** Presumptive evidence for conduction versus excitation failure during pacing from the abnormal epicardium of the infarcted dog heart. Labels are the same as in Fig 5. In panel A pacing from a site in the abnormal epicardium at an RR interval of 270 msec does not result in any marked alteration in the QRS complex however the electrogram recorded from a given site in the abnormal epicardium shows marked fractionation of local activation from beat to beat (note curved arrows). The sudden failure of ventricular activation is characterized by a pacer impulse followed by local activation of the IZeg (straight arrow) suggesting conduction block even though the pacer impulse falls during the refractory period of the ventricles. In panel B from another experiment during ventricular pacing from the abnormal epicardium and an RR interval of 270 msec the IZeg shows relatively constant activation until the beat prior to the block which shows marked prolongation and fractionation of the local ventricular activation. This was followed by a pacer impulse and no recordable activation. Coincidentally no ventricular activation was seen even during the subsequent 2:1 sequence.

ventricle after the sixth beat in the panel despite excitation of the abnormal zone. A complex pattern of delayed electrical activity is seen within the abnormal zone (RR = 220 msec). At times delayed electrical activity can be seen in late diastole (curved arrows). After the sixth beat abrupt loss of ventricular capture occurs with alternate stimuli. On examination of the surface electrocardiogram (L2) it might be supposed that the stimulus occurring early during the T wave failed to excite the myocardium due to absolute ventricular refractoriness. In this case however there is not a failure of excitation within the infarct zone because electrical activity is observed (straight arrow) following the stimulus artifact. Thus there is direct evidence for concealed conduction in the subepicardium over the infarction and also for exit block of conduction in the abnormal zone. Panel B shows another pattern of altered response to regular ventricular stimulation (RR = 270 msec). Infarct zone electrograms are relatively unchanged until abrupt lengthening of conduction time occurs in the sixth beat.

The interval between the pacing impulse and the QRS of beats one through five is 70 msec but abruptly lengthens to 120 msec in the sixth beat. The next stimulus fails to capture.

All dogs demonstrated abrupt failure of ventricular pacing in the manner shown in Figs 5 and 6 from at least one subepicardial site overlying the infarction. Wenckebach conduction delays with resultant exit block and failure of pacing (Fig 5 panel A) was observed in 40% of the studies. Sudden excitation failure with inability of the stimulus to achieve ventricular capture (Fig 5 panel B) occurred in 10% of the dogs. Accurate quantitative assessment of less frequently observed phenomena (e.g. Fig 6 panel B) would however require pacing from multiple infarction zone areas at different rates and stimulus strengths.

The complex and heterogeneous aspects of infarct zone refractoriness are illustrated in Fig 1. Panels A through F depict the response of the ventricle to a premature ventricular stimulus introduced into the subepicardium overlying the infarction during otherwise regular ventricular pacing (RR = 320 msec) from the same stimulation site. The coupling interval of the premature stimulus is gradually shortened from 150 msec (panel A) to 145 msec (panel F). In Panel A the premature stimulus has resulted in ventricular capture. However the configuration of the next beat in the series of regularly paced ventricular beats has altered (fourth beat in panel). In panels B and C the fourth beat becomes less distorted as the coupling interval of the preceding premature beat (third beat) is shortened. This may be explained on the basis of a prolongation of refractoriness outlasting the T wave—i.e. postrepolarization refractoriness resulting from a preceding long short cycle sequence.<sup>11</sup> In this instance the duration of the postrepolarization refractoriness must approximate the interval between beats three and four of panel C. In panel D it can be appreciated that with further shortening of the premature stimulus coupling interval there is obvious prolongation and fractionation of activity recorded in the area of the electrogram (contrast the duration of the IZeg of the premature beat in panels A and D). Prolonged abnormal zone conduction results in a reentrant beat (panel E) with continuous activity recorded by the IZeg. Note in panel E that abbreviated myocardial refractoriness exists as demonstrated by the ability of the stimulus to excite even when introduced

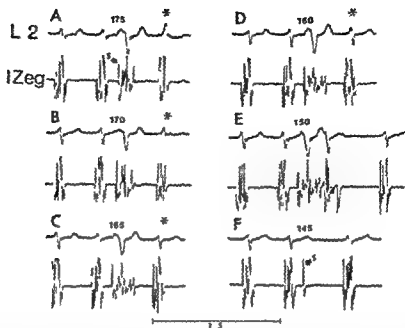


Fig 7 Coexistence of markedly shortened and markedly prolonged refractoriness in the abnormal epicardium of the infarcted dog heart. Two traces, ECG Lead II (L2) and an electrogram from the abnormal epicardium (IZeg) are shown in all panels (A to F). During ventricular pacing from a site within the abnormal epicardium at a cycle length of 370 msec, premature ventricular stimuli (S) are introduced with increasing prematurity, in each consecutive panel. Note in panel A that a premature ventricular beat introduced at a coupling interval of 170 msec shows marked fractionation of the IZeg. In addition, the next driven beat (asterisk) shows a different morphology than the previous QRS at the basic driving cycle length. This effect seen in panels A through D may indicate postrepolarization refractoriness in the abnormal epicardium. In panel E, excitation by a premature ventricular beat at a 150 msec coupling interval occurs even though the stimulus is delivered on the upstroke of the preceding T wave, indicating markedly shortened refractoriness. Thus very early excitation leads to marked fractionation of the IZeg and subsequent reentrant beat (panel E). In panel F at a coupling interval of 145 msec, a period of absolute refractoriness has been approached and no ventricular excitation occurs in response to the premature stimulus.

rior to the onset of the T wave of the preceding beat. Eventually (panel F) at a coupling interval of 145 msec, absolute refractoriness of the abnormal subepicardial muscle is encountered and the stimulus is seen without consequent ventricular capture. Thus the figure illustrates the simultaneous existence of both abbreviated absolute refractoriness of subepicardial muscle within the infarct zone as well as prolonged postrepolarization refractoriness induced by sudden alteration of regular rhythm."

Fig 8 shows *in vitro* observations which relate to some of the preceding *in vivo* findings. A diagrammatic representation of the experiment is shown in the upper left. The stippled area represents the infarct zone (IZ) to which pacing stimuli were applied. Intracellular potentials and electrograms were recorded from the epicardium of normal and infarcted areas (1 and 2 respectively). In panel A, intracellular action potentials and electrograms from both infarct and normal zones

are shown during epicardial pacing over the infarct zone at a cycle length of 800 msec. Even at this cycle length, the IZ intracellular potential shows decreased amplitude and duration in comparison to the IZ action potential. In panel B, the pacing cycle length was shortened to 600 msec. The IZ intracellular potential is markedly deformed and conduction to the NZ is prolonged in comparison to panel A. Note also in panel B in the bottom tracing that the electrogram recorded in the ischemic zone shows no activity apart from a stimulus artifact. This occurs in spite of the close proximity of this electrogram to the microelectrode recording site within the infarct zone epicardium. In panel C, the driving cycle length was shortened further to 400 msec. No activity is recorded in either normal or infarct zone electrograms and the cell in the normal zone remains quiescent. The ischemic zone action potential diminishes in amplitude and duration to the brief response shown in panel C. With further short

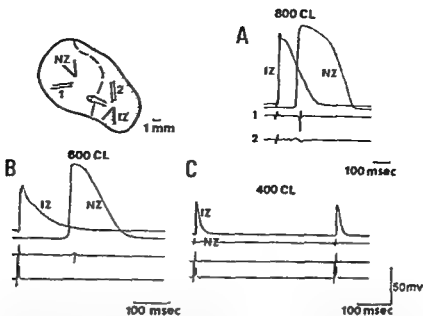


Fig 8 A comparison of the transmembrane action potential record in NZ and IZ from a portion of excised epicardium studied in vitro. The diagram at upper left indicates the extracellular and intracellular recording sites in the NZ and IZ (stippled area). Stimulation was performed from the IZ 1 to 2 mm from the recording sites. In panel A action potentials and electrograms from the IZ and NZ at a cycle length of 800 msec are shown. In panels B and C the pacing cycle length was decreased to 600 and 400 msec, respectively. Note the increasing degree of delay and block between IZ and NZ, as well as the loss of amplitude and duration of the IZ action potential. See text for discussion.

ening of the cycle length the response diminished further gradually, becoming indistinguishable from a stimulus artifact. Further recordings from this experiment are shown in the next figure.

In Fig 9 illustrations are taken from the same experiment as shown in Fig 8. Again in panels A to C pacing is from the abnormal epicardium overlying the infarct zone as shown in Fig 8 and the cycle length is progressively shortened from 320 msec (panel A) to 300 msec (panel B) to 285 msec (panel C). In panel A the four tracings depicted are from top to bottom: infarct zone and normal zone intracellular action potentials and normal zone and infarct zone electrograms. At this cycle length (320 msec) the infarct zone intracellular action potential is markedly abnormal and is seen to be abbreviated both in duration and amplitude when compared to the intracellular recording from the normal zone. Furthermore, a progressive decrease in amplitude and an increase in notching of the abnormal zone action potential is seen in the first four beats of this panel, followed by failure of excitation by the fifth stimulus when only a stimulus artifact is apparent. The sixth stimulus excites, and there appears to be some recovery of the normal zone cell. In panel B the cycle length has been short-

ened further to 300 msec and a 2:1 excitation pattern is seen in the behavior of the cell in this zone. With further shortening of the cycle length to 285 msec in panel C there is higher degree excitation failure with abnormal zone pacing. No extracellular activation is seen after delivery of the first two stimuli. The third stimulus gives rise to a distorted low amplitude and abbreviated action potential within the abnormal zone. Conduction to neighboring areas is noted (lower electrogram) and to the normal zone where healthy intracellular recording and normal electrogram response occurs. In the case of the first and second stimuli in panel C it is uncertain whether or not the intracellular response recorded within the abnormal cell represents an abnormal action potential ("spike potential") or simply a stimulus artifact. The fourth stimulus clearly gives rise only to a stimulus artifact, a delay may represent prolonged (postrepolarization) refractoriness following the abnormal action potential induced by the preceding stimulus.

## Discussion

Reentry as a mechanism of cardiac arrhythmias has been invoked since the experiments of Mayer using the jellyfish umbrella,<sup>1</sup> as cited by

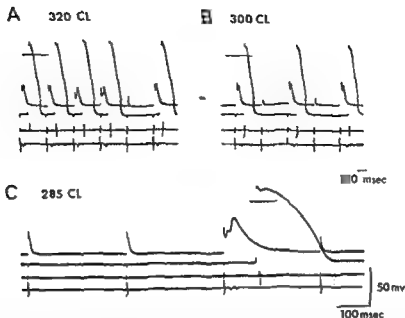


Fig 9 The effects of decreasing cycle length on delay and block between IZ and NZ. In panel A and B at cycle lengths of 320 and 300 msec various degrees of block between IZ and NZ are characterized by diminution of action potential amplitude and duration. In panel C the first two diminutive action potentials under the stimulation electrode do not produce local excitation. Note the presence of IZ electrogram activation associated with a fractionated action potential following the third stimulus. The fourth stimulus is followed by a passive membrane response. See text for discussion.

Crane (see Ref 29 chapter 5). The theoretic criteria for reentry namely slow conduction and unidirectional block were firmly established by the work of Schmitt and Erlanger.<sup>19</sup> Experimentally the work of Moe and associates<sup>20</sup> laid the foundation for the clinical demonstration of reentry whereas the recent work of Wit and colleagues<sup>21</sup> and Anderson and co workers<sup>22</sup> provided clear evidence for reentrant arrhythmias in the His Purkinje system. These latter studies involved the use of normal tissues intoxicated by hyperkalemia and high doses of catecholamines.

Only since 1969 has the evidence been gathered to establish reentry as a mechanism of arrhythmias in ventricular muscle undergoing acute myocardial ischemia.<sup>17, 23</sup> The transient nature of these arrhythmias<sup>24, 25</sup> has not allowed detailed investigation of the alterations in electrophysiological properties responsible for reentry. These reports have emphasized the difficulty in studying such transient phenomena. Studies in our laboratories have described the existence of conduction defects in the epicardium of the infarcted dog heart three to 10 days after coronary artery ligation.<sup>26, 27</sup> Directly associated

with these conduction abnormalities is the spontaneous occurrence of reentrant ventricular arrhythmias which can be induced by various interventions.<sup>28, 29</sup> This electrically stable state of myocardial abnormalities related to infarction permits the systematic study both in vivo and in vitro of the alterations in excitability, conduction and refractoriness<sup>30, 31</sup> underlying reentry in tissue adjacent to areas of recent infarction. It should be pointed out that these findings were determined in sick but viable subepicardium. Recording and pacing from deeper layers indicated dead tissue—i.e. truly infarcted. It would be difficult to call the subepicardium overlying the infarction ischemic since blood flow was not measured. However in vitro the abnormal properties were unchanged even after prolonged periods of superfusion. If superfusion during the microelectrode studies had provided insufficient flow for the abnormal areas these cells would have deteriorated as would those of the normal zone. Neither showed significant deterioration over 3 to 4 hours of study. If in vitro superfusion represented flow over and above perfusion in vivo the abnormal zone might have been expected to have shown steady improvement. This did not

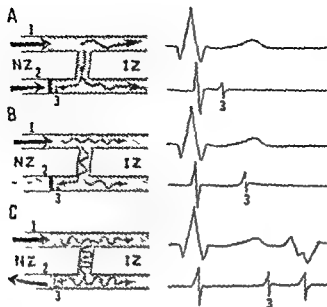


Fig. 3. Schematic representation of functional dissociation of conduction and reentry in two pathways of ventricular muscle. The pathways are labeled 1 and 2 and the electrocardiogram and electrogram recorded at site 3 are shown on the right. The first impulse enters pathways 1 and 2 (panel A) and encounters slow conduction (stippled area) in pathway 1 and total block (solid vertical bar) in pathway 2. In panels B and C the next two impulses entering at pathway 1 encounter progressively slower conduction (note increased tortuosity of pathway 1, high stippled area). In panel C point 3 is a delay enough to allow re-entry. See text for further discussion.

occur. It would appear then that the processes of ischemia and infarction induced as a secondary effect alterations of the electrical properties in those tissues surviving infarction.

Our previous reports utilizing recordings from the epicardium of the infarcted region have provided crucial direct evidence for reentry—a continuous electrical activity bridging the interval between normal and ectopic beats. Also the effect of rate and rhythm to enhance or diminish such continuous activity has been demonstrated.

In the present study pacing from the subepicardium of the infarcted area has allowed further characterization of the electrophysiology of the abnormal tissues. In contrast to pacing from normal myocardium pacing from the abnormal subepicardium manifested unusual responses. At a constant stimulus strength pacing from the same site caused different QRS complexes as a function of pacing rate. Each form of QRS was associated with a different latency—the time from the stimulus to the onset of the QRS complex. Actually, the conduction interval was found to represent a function

within the abnormal subepicardium. Evidence for this view was the increase in duration of the delta wave preceding each type of QRS complex as the heart rate increased (see Fig. 2). Also recording near the stimulating electrode or between the stimulating electrode and the normal zone electrogram showed continuous electrical activity starting at the stimulus and extending up to the onset of the QRS complex (Fig. 1). This fractionated activity was temporally consistent with the delta wave preceding the QRS complex. In vivo the areas of greatest delay as the heart rate was increased were within the abnormal epicardial muscle overlying the infarct zone.

Normal conduction in most areas of the ventricle is dependent on impulse transmission through both fast (His Purkinje system) and slow (ventricular muscle) pathways. Since previous work in the dog with transmural infarction has indicated that muscle underlying the endocardium is inexcitable,<sup>14</sup> and in our studies the deeper subepicardial muscle was also inexcitable it can be assumed that conduction must proceed only through the epicardium which overlies the infarcted muscle as a thin rim of abnormal but viable tissue. This would account for the slow transit time and the delta wave (Fig. 1) preceding the onset of the major QRS deflection—the latter representing more rapid activation via His Purkinje and normal muscle tissue. Some other factors of altered conduction in this area were seen which relate to reentry. Functional dissociation of conducted impulses exiting from the abnormal zone was frequently noted in vivo particularly in response to increasing heart rate. Interestingly in Fig. 3 at a constant heart rate the conduction to each of the electrograms alternated. Such a finding indicates that at least two conduction pathways were involved between the abnormal and normal zones (possibly multiple pathways) at this rate and this could account for the different QRS complexes seen. Furthermore the dissociation of conduction into separate pathways, some of which showed intermittent block, clearly favors reentry. This view has been postulated by Ashman and Hull<sup>15</sup> for myocardial infarction and has been elaborated by Cranefield.<sup>16</sup> Reentry can not occur within an infarct unless there is some partially isolated pathway in which conduction can occur in only one direction. If the island is invaded from all sides by excitatory impulses those impulses may travel very slowly within the infarct but they will eventually collide with each

other and be extinguished without reentering the ventricle. It is for that reason among others that the mere demonstration of delayed excitation within an infarct does not constitute satisfactory evidence that a premature impulse arising near the infarct is caused by reentry via a pathway through the infarct.<sup>18</sup>

Although the evidence for unidirectional block between NZ and IZ was consistently observed, the nature of the block was not easily discerned. Observed frequently, however, was the occurrence of Wenckebach, Mobitz II and paroxysmal (repetitive) forms of block from the IZ to the NZ, particularly as a function of rate. In previous reports the close relationship between delay of epicardial activation in a Wenckebach fashion and the occurrence of reentry beats has been documented.<sup>10-12</sup> Although Wenckebach periodicity can invariably be induced in the normal A-V node during antegrade conduction,<sup>20</sup> it is seldom associated with reentry. If one combines Wenckebach periodicity, repetitive block, and functional dissociation, manifest reentry now becomes easier to construct. In Fig. 10 a schematic representation of a simplified model of reentry is shown. In three successive beats (A to C) at a critical heart rate, conduction velocity progressively slows in pathway 1 (in the form of a Wenckebach cycle) during three beats (A to C). However, at this rate, pathway 2 exhibits repetitive antegrade block (as shown in Figs. 8 and 9) of the impulse (vertical bar). This functional dissociation allows the point labelled 3 to be activated later in the Wenckebach cycle (panel B). When area 3 is activated late enough that its appearance follows the T wave (after the area of repetitive block has repolarized), retrograde invasion of the NZ occurs, resulting in a reentrant beat. Under these circumstances of repetitive (unidirectional) block, the concurrent Wenckebach period will culminate in a ventricular ectopic beat coupled to the sinus beat in a repeatable trigeminy.<sup>21</sup> If on the other hand, there is occasional conduction in pathway 2—i.e., intermittent loss of repetitive block, this intermittent conduction could interfere with the Wenckebach type pattern, thus inhibiting manifest reentry and producing concealed reentry.

Coeexistence of various forms of block were matched by the observation that very short and very long refractoriness could coexist in abnormal tissues. In Fig. 7, late coupled ventricular premature contractions arising in the abnormal zone resulted in a change in the QRS configura-

tion of the next driven beat even though the basic cycle length (330 msec) exceeded the QT interval by 140 msec. This is an example of postpolarization or markedly prolonged refractoriness not observed previously in ischemic myocardium.<sup>18,19</sup> At shorter coupling intervals, marked fractionation and delay were recorded in the IZ electrogram, indicating slow conduction due to activation of some pathways during their relative refractory period. The ischemic zone could be depolarized as early as the onset of the T wave and using stimuli less than two times the diastolic threshold, which is earlier than can be achieved with stimulus intensities between 10 and 12 times threshold prior to the peak of the T wave in the normal heart.<sup>22</sup> In vitro findings of abbreviated action potentials (Figs. 8 and 9) provided one possible explanation for these unusually short refractory periods.

What is the possible significance of this simultaneous but opposing change in refractoriness in the abnormal zone? Firstly, activation during the relative refractory period occurring early or late in the cardiac cycle causes slow conduction (see above) which favors reentry. Recent experimental work in our laboratory was documented the occurrence of reentry, ventricular arrhythmias triggered by late coupled beats as well as by early coupled beats.<sup>23</sup> Clinical reports have now recognized the arrhythmogenic potential of early and late coupled premature ventricular contractions. Secondly, the occurrence of the V on V phenomenon<sup>24</sup> so commonly seen preceding ventricular fibrillation can be explained on the basis of the shortened refractoriness in some areas of the ischemic zone. A recent clinical report<sup>25</sup> clearly documents the very early occurrence of premature ventricular beats even at the onset of the T wave. The coexistence of long and short refractoriness (Fig. 7) is another indication of the marked heterogeneity in the electrophysiological properties of ischemic tissue. Han and Moe popularized the concept of dispersion of refractoriness as an important determinant of reentrant arrhythmias. However, in their studies as well as in more recent work by Levites and associates,<sup>2</sup> the greatest dispersion of refractoriness measured only 40 msec. In the present study, dispersion of refractoriness of at least 150 msec can be appreciated in Fig. 7.

Many of the electrophysiological responses of myocardial cells have been extensively studied only in normal zones. Some of these responses

may be modified in abnormal epicardium overlying infarcted zones. For example the action potentials of myocardial cells in these abnormal areas were often of bizarre configuration (Fig 8). These deformed and fractionated action potential responses have been reported previously<sup>21</sup> and in our experiments these responses showed a rate dependency. In Fig 9 markedly aberrant action potential responses are shown. However conduction to the normal epicardium occurs only when the action potentials at the site of stimulation have an amplitude and duration greater than the abnormal (epicardial) potentials (Fig 8 panel C). This would indicate that severely disturbed cells with abnormal zone are involved in the spread of activation within this area and to the normal zone and are not infarcted cells with no electrical capacities. Fig 9 also illustrates that the heart rate was increased further the more of such cells deteriorated faster and often became difficult to distinguish from a stimulus artifact. The latter is a passive membrane response to the applied stimulus (Fig 9 panel A fifth stimulus) and panel B second and fourth stimuli). However increasing degrees of membrane response were seen at slower rates (abortive action potentials in Fig 8 panel C) and intermittently at higher rates (Fig 9 panel C). These observations represent rate-dependent failure of excitation rather than conduction failure since increasing stimulus strength (Fig 8 A to C) did not prevent action potential diminution at the higher rates.

In conclusion pacing from the subepicardium of the infarcted dog heart in the period three to ten days after coronary artery ligation provides new information regarding altered conduction, refractoriness, and excitability. In addition to underscoring the heterogeneity of the electrical properties of the abnormal tissues, these studies have characterized these disparate properties. In conjunction with unidirectional block coexistence of Wenckebach, Mobitz type II and repetitive forms of block in abnormal muscle can provide possible mechanisms for the common occurrence of reentry in these tissues. In addition the concurrent findings of areas of inordinately long and short refractoriness can help to explain paroxysmal ventricular arrhythmias whose onset is closely coupled to R-T phenomenon or previous sinus beats as well as those initiating late coupled ectopic beats.

## Summary

Reentrant ventricular arrhythmias arise in variable epicardium overlying the transmural infarction zone in the dog 3 to 9 days after ligation of the anterior descending coronary artery. Effects of pacing (90 to 360 beats/minute) from the epicardium in the normal zone and ischemic zone were studied in 18 dogs using standard ECG leads and epicardial recordings. Pacing in the normal zone at any stimulus strength showed no changes in QRS morphology at these heart rates. During pacing at ischemic zone sites, QRS morphology changed with heart rate in association with conduction delays in the ischemic zone. This effect could be reversed by increasing the stimulus strength. Refractoriness in the ischemic zone was tested by programmed pacing. Abnormally short ( $\leq 130$  msec) and long ( $\geq 330$  msec) refractoriness coexisted within the ischemic zone. This marked dispersion of refractoriness was related to the occurrence of reentrant ventricular arrhythmias. In 10 dogs a  $3 \times 4$  cm section of ventricular epicardium was removed which included normal and ischemic zones. Action potentials were recorded during superfusion with Tyrode's solution at  $37^\circ\text{C}$ . Rate-dependent reentrant ventricular arrhythmias were initiated in 90% of the tissue studied. At a constant stimulus strength action potential recorded close to the stimulation site showed progressively shorter ( $< 100$  msec.) diminutive responses as the heart rate was increased. Intermittent failure of excitation was noted at higher rates. Rate-dependent changes in conduction, refractoriness, and excitation are determinants of reentrant ventricular arrhythmia originating in the ischemic zone of epicardium.

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## Ajmaline in WPW syndrome: an electrophysiologic study

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Ajmaline was first isolated as an alkaloid of *Rauwolfia Serpentina*. The first report on ajmaline came from Siddiqui and Siddiqui in 1932.<sup>1</sup> This alkaloid has no sedative, hypnotic, tranquilizing or hypotensive effect of *Rauwolfia Serpentina*. Utility of ajmaline as a potent antiarrhythmic agent was reported first by Arora and Madan.<sup>2</sup> This was further confirmed by reports of others.<sup>3</sup> It has been found to be particularly useful in the management of tachyarrhythmias associated with the Wolff Parkinson White (WPW) syndrome. However, there are very few reports on the electrophysiologic effect of this drug. But the electrophysiologic effect of ajmaline in the WPW syndrome was reported by Wellens and Durrer in a study of four patients. This study was planned to analyze and evaluate the qualitative and quantitative electrophysiologic changes produced by intravenous administration of ajmaline in patients with the WPW syndrome using the technique of His bundle electrography.

### Material and methods

Six patients, three males and three females, in the age range of 24 to 50 years with a mean age of 39 years, formed the material of the study. Three patients had type A and three had type B WPW syndrome in the basal 12 lead electrocardiogram. All patients were symptomatic with recurrent tachyarrhythmias and were referred to this

department for detailed electrophysiologic evaluation. One of them had a recent episode of cardiac arrest. All patients had the details of the study explained to them and informed consent was obtained. All drugs were stopped for at least 10 days before the study, which was conducted in the non-sedated postabsorptive state. His bundle studies were performed as per the technique established in this laboratory, the details of which have been reported elsewhere.<sup>4</sup> In short, a bipolar pacing catheter was introduced percutaneously from the femoral vein using a Seldinger needle and its tip was placed across the tricuspid valve. Two more catheters were introduced from the antecubital vein for right atrial/right ventricular pacing and for recording a unipolar intra atrial (high RA) electrogram (IAE). Two or more surface leads with IAE and His bundle electrogram (HBE) were recorded on an 8 channel photorecording system (Electronics for Medicine DR8 recorder using standard frequency band width). Records were obtained at a paper speed of 100 mm and 200 mm per second with time lines set at 1 second intervals. After the basal 12 lead scalar ECG was recorded, the control electrophysiologic parameters were obtained in all patients. Rapid atrial and ventricular pacing was done using a KM cardiac pacemaker/overdrive pacemaker with a pulse width of 1 msec. These studies confirmed the usual electrophysiologic characteristics of the WPW syndrome. Fifty milligrams of ajmaline was injected intravenously over a 10 second period and records were obtained at 30 seconds, 1 minute through 15 minutes at the interval of 1 to 2 minutes and at 20, 25, 30, 45 and 60 minute intervals in patients who showed persistent electrocardiographic and

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Table I

Patient initials	PR interval		PA		AH		HV		QRS	
	Before	After	Before	After	Before	After	Before	After	Before	After
Z.	90	10	10	10	90	110	-10	+50	90	90
C.L.	90	190	30	30	70	80	-10	+70	140	80
A.N.	100	110	0	0	100	100	0	+10	110	70
R.R.	100	140	20	20	60	80	-10	+40	115	80
P.J.	80	180	15	90	80	100	-10	+50	120	80
J.S.	130	200	20	30	110	120	0	+50	110	90
Mean	99.16	166.9	16.7	19.1	90	100	-7.5	+4.8	119.16	81.6
P value	P 0.01		P 0.005		P 0.01		P 0.01		P 0.02	
Significance	highly significant		not significant		highly significant		highly significant		significant	

All values in msec.

electrophysiologic alterations produced by ajmaline. In addition in three patients two with narrow QRS and one with broad QRS tachycardia the drug was given during the arrhythmia while continuous records were obtained. Blood pressure was also recorded to detect any hypotension. During complete blockade of the bypass pathway when a normal QRS interval was restored a 12 lead scalar ECG was recorded for comparative studies. All resuscitative measures were kept in a standby condition.

### Results

All six patients studied had manifest ECG evidence of bundle of Kent operation (Type A in three and type B in three) during sinus rhythm. Electrophysiologic features were consistent with WPW preexcitation and pseudo WPW presentation due to simultaneous James and Mahaim preexcitation was ruled out.

The details of electrophysiological effects of ajmaline are summarized in Table I. No significant change in sinus rate was encountered following ajmaline administration. PR prolongation was common to all with mean PR interval rising from 99.16 to 166.9 msec (Fig 1). In none did the PR interval increase beyond the normal range and the range of increase was from 10 to 100 msec. Mean PJ interval demonstrated an increase from 210 msec. to 238 msec after ajmaline. Mean QRS duration showed a decrease from 119.16 msec to 81.6 msec (Fig 2).

There was no appreciable alteration of the PA interval and the AH interval was only marginally affected, mean AH rising from 90 msec to 100 msec (Fig 3). These effects of ajmaline lasted for

10, 20, 30, 40 and 60 minutes in the patients studied.

The most striking electrophysiologic observation was HV prolongation following ajmaline administration implying resumption of normal AV nodal His conduction (Figs 4, 5 and 6). The increase in HV interval ranged from 10 to 80 msec with the mean HV interval rising from -7.5 msec before the drug to +45.8 msec after it (Fig 4). The effect on the HV interval appeared within 30 to 60 seconds of administration of the drug and persisted for 15 to 60 minutes.

Rapid atrial and ventricular pacing following ajmaline confirmed complete blockade of anomalous pathways in four patients. Atrial pacing produced progressive lengthening of AH interval till AH Wenckebach block occurred with the HV interval remaining unaltered. Ventriculoatrial conduction which could be elicited in all subjects before giving ajmaline was abolished following the drug.

In three patients in whom tachycardia could be induced (broad QRS in one and narrow QRS in two) intravenous ajmaline was successful in restoring them to sinus rhythm within 15 seconds of administration (Figs 7 and 8). Tachycardia could not be induced in any after ajmaline had been given.

### Discussion

Even though nearly half a century has elapsed since its discovery yet the antiarrhythmic electrophysiologic effects of ajmaline have not yet been precisely defined. While reporting their results in experimental animals Obayashi and associates observed that any effects on conduc-

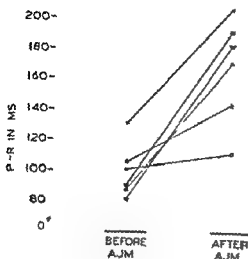


Fig 1 PR interval in six patients with WPW syndrome before and after ajmaline administration

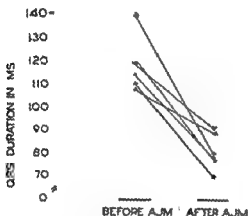


Fig 2 This graph shows the decrease in QRS duration produced by intravenous ajmaline

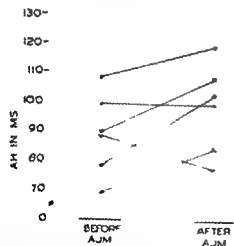


Fig 3 This graph shows the effect of intravenous ajmaline administration on the AH interval in four patients with WPW syndrome. In these patients, the AH interval was prolonged and shows a marginal decrease in one patient after treatment.

tion intervals were forthcoming only if the drug was administered in high dosages.

Ajmaline has been shown to impair conduction and to cause block in the bypass pathway in patients with WPW. Wellens and Durrer<sup>1</sup> found that of four patients with WPW, three developed temporary complete blockade of the accessory pathway (AP) and the fourth patient showed a marked increase in the refractory period of AP. As a result of this normalization of the QRS interval occurred with abolition of the delta wave and restoration of normal ventricular depolarization. There is a prolongation of the HV interval without a concordant increase of the AH interval. It is given during tachycardia the same can be abolished though junctional tachycardias have been reported even after normalization of the QRS interval following ajmaline. Wellens and Durrer<sup>1</sup> also reported loss of ability to initiate tachycardia by single stimulus following ajmaline an increase in the refractory period of atrium and ventricle and increased VA conduction time following ajmaline. These effects of the drug have been reported to last from 15 to 45 minutes.

Ajmaline has been found to shorten the action potential duration and refractory period in normal Purkinje fibres. Obayashi and colleagues<sup>2</sup> observed that the main mechanism was suppression of intraventricular conduction and therefore the drug was effective in reentrant tachycardias. Chiale and co-workers<sup>3</sup> have concluded that the anomalous bundle is inherently diseased and allows ajmaline to block conduction through it. Their studies showed that in the dosage used (70 mg in a single intravenous injection) ajmaline did not cause bundle branch block in normal subjects whereas such block could readily be elicited when the bundle branch system was previously diseased. They pointed out that ajmaline specifically causes prolongation of the range of phase 3 and phase 1 block, both at the expense of the intermediate normal conduction range.

In the present study all patients who showed WPW pattern in sinus rhythm showed quick reversion to normal AV nodal His conduction. Complete blockade of the accessory pathway has been reported by Wellens and Durrer<sup>1</sup> and also Puech and colleagues.<sup>4</sup> HBF findings were consistent with the change in conduction pattern i.e. prolongation of the HV interval. On three occasions narrow and broad tachycardias were successfully abolished with ajmaline administration.

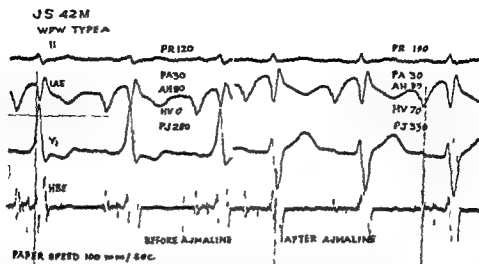


Fig 4 Basal electrophysiological parameters in a patient with type A WPW syndrome before ajmaline (left side panel) IAE represents high RA intra atrial electrogram HBE represents His bundle electrogram. A PR interval of 120 msec may suggest first-degree block at the bypass pathway. After ajmaline (right side panel) there is a total change in ECG Lead V<sub>1</sub> with abolition of the delta wave and an HV interval increasing to 70 msec from a basal of 0

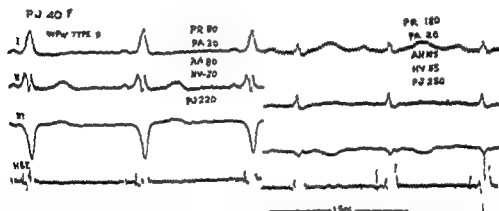


Fig 5 ECG Leads I, II, III and His bundle electrogram of a patient of WPW syndrome type "B" during basal normalization (left side panel), an HV interval of -20 msec is changed to +50 msec after ajmaline. This is due to normalization of AVN-His conduction system with blockade of the bypass pathway. This is also reflected in the increase in PR interval and decrease in QRS duration after ajmaline.

tion. Similar effects were observed by Homola and Srnoga.<sup>10</sup> Spontaneous tachycardias following ajmaline as reported by others were not encountered in any patients and we were also unable to induce tachycardia by atrial or ventricular pacing after ajmalization. VA conduction which was present in all patients was universally abolished following the drug, though Wellens and Durrer<sup>11</sup> could elicit VA conduction in one patient following ajmaline with prolonged VA time. That ajmaline has no appreciable effect on AH has also been pointed out by others.

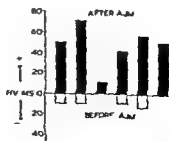


Fig 6 Bar diagram showing basal HV and HV intervals after ajmaline administration in six patients with WPW syndrome.

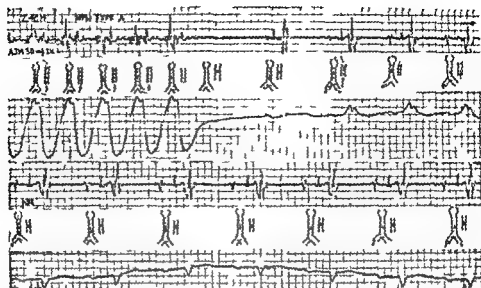


Fig 7 Continuous tracing depicting HBE and Lead V during broad QRS tachycardia at a rate of 200/minute indicating antegrade conduction through the bypass pathway as shown by the absence of His deflection preceding V potential and retrograde conduction via the A-V node as confirmed by retrograde His deflection. The tachycardia is terminated by ajmaline by abolishing AV conduction along the bypass pathway as shown by the last A deflection. This is not followed by a V potential. The first beat following cessation of tachycardia is sinus conducted with an AH interval of 60 msec and an HV interval of 40 msec. The next three complexes are fusion beats with AH interval of 100 and an HV interval of +20 msec. The lower part of the continuous tracing shows all sinus beats with an AH interval of 130 msec and an HV interval of 60 msec.

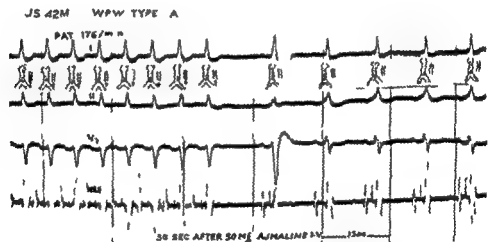


Fig 8 This tracing shows Leads I, II, V, and HBE demonstrating narrow QRS reentrant tachycardia implying antegrade conduction through the A-V node and retrograde conduction through the bypass pathway. Within 30 seconds of ajmaline administration the reentrant tachycardia is abolished by blocking VA conduction due to prolongation of the refractory period of the bypass pathway. The first beat following cessation of tachycardia is a sinus beat conducted with an AH interval of 100 msec and an HV interval of 30 msec, with depressed intraventricular conduction time with a wide QRS. The subsequent complexes show fusion beats with the same AH and HV intervals (paper speed 25 mm/sec).

One shortcoming of ajmaline is its short duration of action which in the present study ranged from 15 to 60 minutes (mean 30 minutes). In a similar study by Durrer<sup>4</sup> the effect of ajmaline lasted 45 minutes. However Chial<sup>5</sup> observed that the intensity and duration of the effects of ajmaline were more marked if the conduction system was already diseased (an effect lasting from several hours to 1 to 2 days). The effectiveness of ajmaline in WPW therefore may be due to a diseased state of the

observed that the intensity and duration of the effects of ajmaline were more marked if the conduction system was already diseased (an effect lasting from several hours to 1 to 2 days). The effectiveness of ajmaline in WPW therefore may be due to a diseased state of the

anomalous bundle. Two of our patients have been free of paroxysmal tachycardias for the past 6 months while on oral ajmaline in the dose range of 150 to 300 mg/day.

### Summary

Six patients including three females with WPW syndrome (three with type A and three with type B) presenting with recurrent paroxysmal tachyarrhythmia were subject to electrophysiological studies. Apart from basal parameters, rapid atrial and ventricular pacing was done which confirmed electrophysiological characteristics of bundle of Kent operation. A single intravenous bolus of ajmaline 50 mg was effective in blocking the bundle of Kent in all patients within 30 seconds of injection with the effect persisting for 15 minutes in one and from 25 to 60 minutes in the others. The most dramatic effect was prolongation of the HV interval with normalization of QRS complex with a marginal effect on the AH interval. The drug was also effective in breaking narrow QRS tachycardia in two patients and broad QRS tachycardia in one patient. Long term oral therapy with ajmaline has proved effective in preventing recurrent tachyarrhythmias.

We conclude that ajmaline is specifically effective and safe in the treatment of the WPW syndrome.

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# Submaximal exercise testing after unstable angina\*

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Data obtained in the last few years have shown that the risk of death or myocardial infarction after unstable angina is lower than had been previously suspected.<sup>1,2</sup> Nevertheless for several months after an episode of unstable angina the risk of fatal or morbid events is higher than during stable angina pectoris. About one third of patients with unstable angina later develop intractable angina pectoris or have recurrent unstable angina. While some clinical features are associated with a poor outcome for these patients in general attempts to accurately predict death and myocardial infarction for individual patients with unstable angina have proved unsuccessful.<sup>3</sup> Furthermore little information is available regarding the prediction of patients who subsequently develop severe stable angina pectoris or recurrence of their unstable angina.

While several reports have suggested that unstable angina constitutes an acute emergency requiring prompt cardiac catheterization and bypass surgery for optimal therapeutic results randomized controlled trials have not supported this view. In the light of the risks and costs

accompanying cardiac catheterization and coronary artery bypass surgery the evaluation of a noninvasive procedure that may assist the clinician in the management of the individual patient with unstable angina appears warranted.

The value of the exercise test in the diagnosis and functional evaluation of the patient with stable angina pectoris is well established.<sup>4,5</sup> Recent reports have demonstrated the value of exercise testing after acute myocardial infarction.<sup>6,7</sup> Similar studies have not been reported in patients following unstable angina. This study was carried out in patients with unstable angina to determine (1) whether submaximal exercise testing prior to hospital discharge is a safe procedure and (2) if the exercise test may be useful in the identification of those patients likely to experience further events of myocardial ischemia soon after hospital discharge.

## Materials and methods

**Patient selection** Unstable angina was defined as worsening of previous angina pectoris or the new onset of progressive angina pectoris within four weeks prior to presentation to the hospital. A diagnosis of ischemic heart disease was required and established by one or more of the following criteria: (1) previous documented myocardial infarction; (2) electrocardiographic evidence of myocardial ischemia ( $> 1$  mm of horizontal or downsloping ST segment depression sustained for 0.08 sec beyond the J point); (3) previous positive maximal exercise test; (4) documented disease by coronary arteriography; or (5) a previous history of typical angina pectoris. Patients with possible precipitating events or concurrent disease were

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excluded. Patients who developed an acute myocardial infarction were also excluded. Acute myocardial infarction was documented by diagnostic QRS changes and/or ST segment and T wave abnormalities on the electrocardiogram consistent with myocardial ischemia associated with elevation of any two of the three cardiac enzymes (creatinine kinase, glutamic oxaloacetic transaminase or lactic dehydrogenase) to at least twice the upper limits of normal. Only patients fulfilling these above criteria and who responded to medical therapy were considered for study. Response to medical therapy was adequate if the patient was pain free or returned to the previous pattern of chronic stable angina pectoris during his hospitalization.

Sixty-one consecutive male patients, ages ranging from 42 to 70 years and mean age 56 years, admitted to the coronary care unit were studied. Forty-two of the 61 patients were receiving oral propranolol therapy at the time of the submaximal exercise test. Each test was performed a few days prior to discharge and at least 3 days and usually one week after their last episode of angina. Informed consent was obtained from each patient. The test was supervised by a physician and a specially trained technician.

Follow-up data were available on 55 patients over a period of 5 to 36 weeks (mean 18 weeks) after hospital discharge. Exercise tests symptom limited or targeted to 90% of the patients predicted maximal heart rate were obtained on 31 patients within 20 weeks (mean 10 weeks) of hospital discharge.

**Exercise testing.** Exercise was performed on a Monark bicycle ergometer. The electrocardiogram was continuously monitored on a Hewlett-Packard 1516A tape terminal attached to a Hewlett-Packard 1309A oscilloscope using a modification of Frank's orthogonal lead system.<sup>1</sup> Permanent recordings at 25 mm/sec were made before exercise, during the last 30 seconds of each level of exercise obtained and during the first 30 seconds of each post-exercise minute of observation (5 minutes or until return to pre-exercise status). Indirect blood pressure recordings were obtained at one minute intervals throughout the study by the Doppler technique using an Arteriosonde (Roche). Each patient commenced exercise at 150 kpm/minute, increasing by increments of 150 kpm/minute every 3 minutes until the individual endpoint was reached.

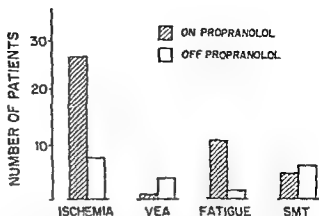


Fig 1 Numbers of patients on and off propranolol who prematurely terminated their submaximal exercise test due to chest pain and/or significant electrocardiographic changes (ISCHEMIA), ventricular ectopic activity (VE4), or fatigue or achieved the target heart rate of 120 beats/minute (SMT).

The submaximal exercise test was targeted to a heart rate of 120 beats per minute. Indications for premature termination of exercise in our laboratory have been described elsewhere and include typical angina pectoris, electrocardiographic ST segment changes of 1 mm or greater, exercise hypotension and ventricular ectopic activity of Grade 2 or higher (that is more than three unifocal ventricular premature beats per minute, multifocal ventricular premature beats, ventricular couplets or tachycardia, or the R on T phenomenon).<sup>1-3</sup> Otherwise if it was not prematurely terminated by patient fatigue, the exercise test was discontinued at the target heart rate.

**Statistical analysis.** Data were evaluated by chi-square analysis and by analysis of variance.<sup>1</sup>

## Results

The reasons for terminating the maximal exercise tests are shown in Fig 1. In no patient was recurrence of unstable angina or acute myocardial infarction precipitated by the exercise test. Exercise was terminated by an evidence of myocardial ischemia (chest pain and/or significant electrocardiographic ST segment changes) in 34 patients (56%); 26 of whom were receiving propranolol. Fourteen patients had electrocardiographic changes alone, 10 patients had both chest pain and electrocardiographic changes, and 10 patients had chest pain only. Premature termination of the exercise by ventricular ectopic activity



Table I Hemodynamic levels at termination of submaximal exercise (mean  $\pm$  SE)

	On propranolol (n = 32)	Off propranolol (n = 19)	p
Heart rate (beats/min)	99 $\pm$ 2	110 $\pm$ 4	< .01
Work load (kpm/min)	349 $\pm$ 24	234 $\pm$ 31	< .01
Heart rate $\times$ systolic blood pressure/100	141 $\pm$ 3	136 $\pm$ 4	NS

Abbreviations: kpm/min = kilopond meters per minute; p = probability

Table II Clinical status of 55 patients in whom follow up data were available compared to reasons for termination of pre discharge submaximal exercise

NYHA Class	All patients			On propranolol			Not on propranolol		
	I or II	III	IV	I or II	III	IV	I or II	III	IV
Number of patients	27	5	23	22	3	15	5	0	8
Significant electrocardio- graphic changes $\pm$ chest pain	8	3	17	7	1	10†	1	2	8
Chest pain only	4	1	3	4	1	3	0	0	0
Fatigue	10	0	2	9	0	2	1	0	0
Achieved target heart rate	5	1	1	2	1	0	3	0	1

p < 0.001.

†p < 0.05.

NYHA Class = New York Heart Association Classification

occurred in only five patients (8%). Three of the five patients had multifocal ventricular premature beats, one of whom had ventricular couplets and two patients had unifocal ventricular premature beats at greater than 3 per minute. Only one of these five patients was on propranolol therapy. Thirteen patients (21%) spontaneously terminated their tests because of leg fatigue. 11 of these were receiving propranolol. Only nine patients reached their target heart rate of 120 beats/minute, four of whom were on propranolol therapy.

The mean values of heart rate, work load, and double product (heart rate  $\times$  systolic blood pressure/100) at the termination of exercise are shown in Table I. In patients on propranolol, mean peak heart rate (99  $\pm$  2 beats/minute, p < 0.01) was lower and mean threshold work load (349  $\pm$  24 kpm/minute, p < 0.01) was higher than those off propranolol (heart rate 110  $\pm$  4 beats/minute, work load 234  $\pm$  31 kpm/minute). Mean values for double product were similar in both groups.

The clinical status of the 55 patients in whom follow up data were available was divided into three groups. Twenty-four patients (44%) had no

further chest pain or only mild angina pectoris (NYHA Class I and II). Five patients had further episodes of severe but stable angina pectoris (NYHA Class III). Twenty-three patients had further episodes of unstable angina and/or intractable angina pectoris (NYHA Class IV). The reasons for termination of the submaximal exercise tests in these patients are shown in Table II. Forty patients were receiving propranolol therapy at the time of their exercise test. Of 23 patients with NYHA Class IV angina, 17 patients (74%) had the exercise tests prematurely terminated by significant electrocardiographic changes (either significant ST segment changes or ventricular ectopic activity) with or without associated chest pain (p < 0.005). This significant finding persisted in Class IV angina patients receiving propranolol: 10 of 15 patients (67%) on propranolol had significant exercise induced electrocardiographic changes (p < 0.01). Eight patients (35%) with NYHA Class I and II angina and three patients (60%) with NYHA Class III angina had their exercise tests prematurely terminated by electrocardiographic changes.

Thirty-one patients had maximal stress tests performed within 20 weeks of hospital discharge.

Table III Response to symptom limited exercise in patients who had both pre discharge and post discharge studies (Mean  $\pm$  SE)

Time of test	Number of patients	Heart rate (beats/min.)	Work load (kpm/min.)	Systolic BP (mm Hg)	RPP	Evidence of ischemia
Pre-discharge (submaximal)						
All patients	28	98 $\pm$ 2	310 $\pm$ 24	142 $\pm$ 3	136 $\pm$ 4	20(71%)
On propranolol	20	95 $\pm$ 3	335 $\pm$ 29	143 $\pm$ 4	132 $\pm$ 4	13
Not on propranolol	8	104 $\pm$ 5	246 $\pm$ 40	140 $\pm$ 4	145 $\pm$ 8	7
Post-discharge (maximal)						
All patients	28	104 $\pm$ 4	397 $\pm$ 25	141 $\pm$ 3	147 $\pm$ 7	18(64%)
On propranolol	25	103 $\pm$ 4	306 $\pm$ 36	143 $\pm$ 3	148 $\pm$ 8	15
Not on propranolol	3	113 $\pm$ 11	295 $\pm$ 75	128 $\pm$ 9	144 $\pm$ 11	3

Chest pain a d/or significant electrocardiographic changes

Abbreviations kpm/min. = kilopond meters/minute BP = blood pressure RPP = rate-pressure product (heart rate  $\times$  systolic blood pressure/100)Table IV Response to exercise at constant workloads of 150 kpm/min in 24 patients and 300 kpm/min in 15 patients (mean  $\pm$  SE)

Workload (kpm/min.)	Time of test	Heart rate (beats/min.)	Systolic BP (mm Hg)	RPP	Evidence of ischemia
150	Predischarge (submaximal)	87 $\pm$ 9	12 $\pm$ 2	110 $\pm$ 3	2(8%)
	Postdischarge (maximal)	86 $\pm$ 3	109 $\pm$ 3	113 $\pm$ 4	1(4%)
300	Predischarge (submaximal)	95 $\pm$ 3	141 $\pm$ 3	134 $\pm$ 4	5(33%)
	Postdischarge (maximal)	104 $\pm$ 3	141 $\pm$ 3	147 $\pm$ 9	3(20%)

Chest pain and/or significant electrocardiographic changes at given workload

Abbreviations BP = blood pressure kpm/min. = kilopond meters per minute

RPP = rate pressure product (heart rate  $\times$  systolic blood pressure/100)

Three of these patients reached the target heart rate of 120 beats per minute during their pre discharge submaximal exercise tests. Comparative exercise data for the remaining 28 patients who had symptom limited pre-discharge and post-discharge tests are shown in Table III. No significant changes occurred in threshold heart rate, work load, systolic blood pressure, or rate pressure product in all patients, or when patients on and off propranolol were considered separately. Furthermore, the number of patients with evidence of exercise induced myocardial ischemia (significant ST segment changes and/or chest pain) did not change significantly between pre-discharge submaximal and post-discharge maximal studies. Of the 20 patients (71%) who had ischemic responses during their pre-discharge studies, 16 had similar responses during their post-discharge study; two patients who had pre-

maturely stopped with fatigue in their first study subsequently had their post-discharge study prematurely terminated by an ischemic response. Twenty patients were receiving propranolol at the time of their pre-discharge test and five additional patients were receiving the drug at the time of their post-discharge maximal test.

The serial response to exercise at constant workloads of 150 kpm/minute in 24 patients and 300 kpm/minute in 15 patients is shown in Table IV. The remaining patients failed to achieve these workloads during either their pre-discharge or post-discharge exercise tests. No significant changes at either workload occurred in heart rate, systolic blood pressure, or rate pressure product. The incidence of exercise induced myocardial ischemia at each given workload was lower in the post-discharge studies, but the reduction was not significant.

## Discussion

The risks of exercise testing in patients with stable angina pectoris have been previously reported.<sup>10</sup> The roles of submaximal and maximal exercise testing following acute myocardial infarction have been studied in several centers recently and were demonstrated to be of value in the assessment of functional capacity and the suitability of rehabilitation in these patients.<sup>11,12</sup> No similar data are known to us however regarding patients following unstable angina. While the numbers of patients are too few to permit precise conclusions, the results of this study suggest that under the strict criteria incorporated in our study protocol submaximal exercise testing soon after unstable angina is not a hazardous procedure.

While several clinical features have been implicated as predictors of death or myocardial infarction following unstable angina, predictors of the severity of subsequent angina have not been extensively sought out.<sup>1,2,23,24</sup> It has been reported that as many as one third of patients with unstable angina develop subsequent episodes of unstable angina or intractable angina pectoris. While not dealing with death or myocardial infarction, the results of our present study suggest that submaximal exercise testing provides useful prognostic information regarding subsequent angina in patients who stabilize on medical therapy. The occurrence of exercise induced electrocardiographic changes on the submaximal exercise test appears to predict an unfavorable clinical course after hospital discharge and may thus be of aid in selecting patients for early coronary artery bypass surgery.

The role of coronary artery surgery after unstable angina remains controversial. Randomized controlled prospective trials have shown that surgical intervention soon after unstable angina is effective in decreasing the frequency and severity of angina but does not reduce the incidence of death and appears to increase the risk of myocardial infarction. Because of these findings it has been suggested that patients with unstable angina should be stabilized with medical therapy, if possible, deferring a decision regarding surgical therapy until the severity of the patient's subsequent angina has been established. On the other hand it has been shown that despite the substantial costs of bypass surgery, the present hospitalization of patients with unstable angina or intractable

and receive only medical therapy may equal or even exceed the costs of surgery.<sup>25</sup> Thus, a method of predicting the subsequent severity of angina in these patients after hospital discharge may help to resolve the dilemma of management of patients who stabilize on medical therapy after unstable angina.

Four of the five patients whose tests were terminated because of exercise induced ventricular ectopic activity were not receiving propranolol therapy. Propranolol has been shown in our laboratory to reduce the frequency of exercise induced ventricular ectopic activity in patients with chronic ischemic heart disease and in particular the high grades of ventricular ectopic activity.<sup>21</sup> Although the numbers of patients are small, precluding definitive conclusions in these patients with unstable angina, this study suggests that propranolol has a protective effect in reducing the incidence of exercise induced ventricular ectopic activity following unstable angina. Furthermore, propranolol therapy did not significantly affect the frequency of an exercise induced ischemic response in these patients. Previous studies in our laboratory have shown that while the frequency of an exercise induced ischemic response is reduced by propranolol in patients with two vessel coronary disease it is not affected by propranolol in patients with three vessel or left main disease.<sup>2</sup> The data in our present study suggest that these patients with unstable angina have more severe coronary artery disease agreeing with the previous study of Allison and colleagues<sup>26</sup> on similar patients.

It has been reported in patients who underwent serial exercise tests following an acute myocardial infarction that there are both early and late phases of improvement in the impaired cardiovascular function resulting from the infarction.<sup>2</sup> The improvement was determined by clinical and electrocardiographic estimates of the threshold of myocardial ischemia including exercise induced chest pain or electrocardiographic changes, peak work load or peak heart rate, blood pressure product. Similar analysis of serial exercise data of our patients after unstable angina showed no significant changes in clinical or electrocardiographic estimates of myocardial ischemia at either maximal symptom limited exercise or at differing constant workloads. These data suggest that should impaired cardiovascular function occur during unstable angina, any recovery in function occurs

soon after stabilization on medical therapy and before the pre discharge submaximal exercise test has been performed.<sup>36</sup>

In conclusion the results of the present study demonstrated that submaximal exercise testing soon after unstable angina is not a hazardous procedure if the test is closely monitored and promptly terminated by well defined criteria. While numbers were small, propranolol appears to have a protective effect in reducing the incidence of exercise induced ventricular ectopic activity. Exercise induced abnormal electrocardiographic changes in pre discharge submaximal exercise tests significantly predicted further episodes of unstable angina in a mean follow up period of 18 weeks. Comparison of serial exercise data from pre discharge submaximal and post discharge maximal exercise tests suggested that any recovery in cardiovascular function after unstable angina occurs soon after stabilization and prior to the pre discharge submaximal test.

#### Summary

Sixty one consecutive men, mean age 56 years, who fulfilled criteria for unstable angina and who responded to medical therapy underwent submaximal exercise testing prior to hospital discharge and at least 3 days after their last episode of angina. Forty two patients were receiving propranolol at the time of exercise. Submaximal exercise was targeted to 120 beats/minute and strict criteria for the premature termination of each study were followed. Follow up data were available on 55 patients post discharge over a period of 1 to 36 weeks.

No patient suffered recurrence of unstable angina or myocardial infarction due to the exercise test. Exercise was prematurely terminated by an ischemic response (chest pain and/or ST segment changes) in 34 patients (56%) and by leg fatigue in 13 patients (21%). Only five patients had exercise induced ventricular ectopic activity, four of whom were not receiving propranolol. Nine patients achieved the target heart rate. Exercise induced abnormal electrocardiographic changes predicted the postdischarge recurrence of episodes of unstable angina ( $p < 0.05$ ). Comparison of pre-discharge submaximal exercise data with postdischarge maximal exercise shows that recovery in cardiovascular function after unstable angina occurs soon after stabilization and prior to the submaximal test.

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## Laennec's cirrhosis and primary pulmonary hypertension\*

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There have been few reports<sup>1-4</sup> of the rare association of cirrhosis and primary pulmonary hypertension. This case report adds to the literature a well-documented case of the foregoing and also reviews the literature.

### Case report

The patient is a 40-year old female who was born and raised in France. With each meal she consumed a half bottle of wine. She was entirely well until 1968 when at age 30 she presented with a complaint of amenorrhea. Physical examination revealed hepatosplenomegaly. An upper gastrointestinal study demonstrated a duodenal ulcer which was managed medically. In 1970 the patient had acute bleeding of the upper gastrointestinal tract. After medical stabilization a liver biopsy was performed (Fig 1). It documented a marked increase in connective tissue surrounding pseudolobules with bile duct proliferation. There was chronic inflammation but no definite alcoholic hyaline. There was one focus of acute inflammation in the parenchyma. No pigment accumulation was present. Copper stains were negative. HB Ag, fluorescent antinuclear antibody, and serum protein electrophoresis were unremarkable. This was felt to be consistent with nutritional or Laennec's cirrhosis. The patient was subsequently readmitted on multiple occasions for upper gastrointestinal tract bleeding.

In 1977 after another episode of bleeding in the upper gastrointestinal tract endoscopy demonstrated numerous esophageal and gastric varices. Peritoneoscopy revealed a

prominent accessory hepatic lobe. The liver surface was pale and uniformly studded with millet seed like lesions representing dilated lymphatic ductules. Neovascularization over the surface of all three lobes was noted. Coarse nodularity in addition to micronodularity was also noted on both anterior and inferior liver surfaces. A portacaval shunt was discussed but was not felt to be warranted at this time. Her dyspepsia, iron deficiency anemia, and trace ascites were respectively managed with antacids, iron, and diuretics with good results.

During this admission the patient was noted to have a systolic murmur and ejection click. The patient was referred to the Cardiology Service for further evaluation. The patient denied any history of rheumatic fever, effort syncope, chest pains, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, cyanosis, or edema. The patient has one child, a daughter who is 21 years old, alive and well. The patient has smoked a half pack of cigarettes per day over the last 20 years. There was no history of diabetes, hypertension, use of oral contraceptives, anorectic agents, or exposure to any tropical diseases.

Physical examination revealed a jaundiced female with a cardiac examination consisting of a palpable S<sub>1</sub> and an increased P of the second heart sound. There was an ejection click heard best at the second right intercostal space increasing with expiration. There was a systolic ejection murmur heard best at the second left intercostal space. Grade II increasing with inspiration. The P was equal to A. There were no diastolic murmurs, gallops, bruits, cyanosis, or edema. Abdominal examination revealed a liver of 14 cm in span and a palpable spleen tip. There was no ascites.

The electrocardiogram (Fig 2) in 1978 demonstrated early R wave progression suggestive of right ventricular hypertrophy (RVH) with right axis deviation. The vectorcardiogram was consistent with type C RVH. The echocardiogram revealed normal septal motion, a normal "a" dip in the pulmonic valve and evidence of right ventricular dilatation. The chest x ray (Fig 3) demonstrated right ventricular enlargement and prominent pulmonary artery segments bilaterally.

The cardiac catheterization data are recorded in Table I. At cardiac catheterization severe pulmonary hypertension was found. There was no gradient across the pulmonic valve. Saturations on pullback revealed no step-up. Hydrogen

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Fig 1 Increased connective tissue around pseudolobules with bile duct proliferation and chronic portal inflammation consistent with Laennec's cirrhosis

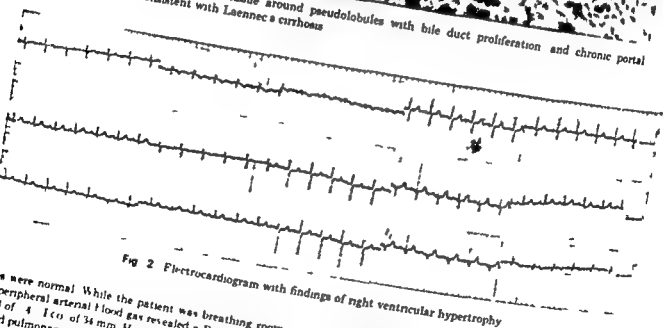


Fig 2 Electrocardiogram with findings of right ventricular hypertrophy

... were normal. While the patient was breathing room air, peripheral arterial blood gas revealed a  $P_{O_2}$  of 77 mm Hg and  $P_{CO_2}$  of 34 mm Hg and  $SO_2$  of 94%. Because of the patient's respiratory distress, a pulmonary artery catheter was inserted and a pulmonary artery pressure was obtained. However, a manual injection of dye into the pulmonary artery demonstrated no evidence of peripheral vascular disease. Studies were performed including a chest x-ray and a mesenteric arteriogram. Small pancreaticoduodenal arteries were noted in the head of the pancreas. The hepatic vessels, including the portal vein, were normal.

There was no evidence of neoplasm. The splenic vein was noted to be patent. The portal vein was not visualized on the superior mesenteric arteriogram. The perfusion lung scan demonstrated a patchy distribution as well as a specific isolated sub-segmental defect in the upper posterior aspect of the left lung which later filled. This was consistent with multiple emboli. Complete pulmonary function tests revealed a mild obstructive ventilatory defect with increased residual volume. A multiple gated acquisition scan revealed the left ventricle to have a decreased volume, a hyperkinetic wall motion, and an ejection fraction of 60%.

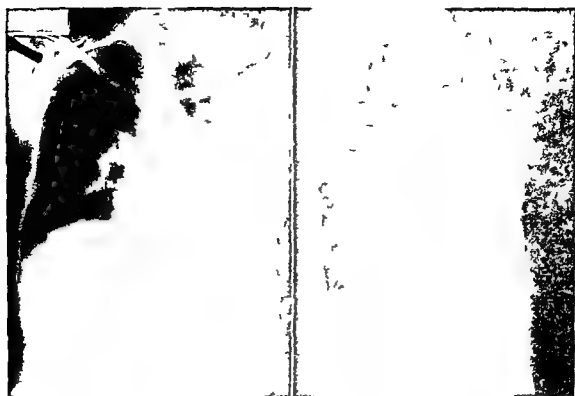


Fig 3 Chest x ray with prominent pulmonary artery segments bilaterally and RVH (posteroanterior [left] and lateral [right] films)

## Discussion

There are many ways in which hepatic disease influences the general circulation. Hemodynamic measurements have revealed abnormalities in patients with cirrhosis. These include tachycardia, reduced arterial oxygen saturation, diminished cardiac output, widened pulse pressures, expanded blood volume, reduced vascular resistance, and shortened circulation time. Hepatic artery oxyhemoglobin saturations have been found to be less than 94%. Venous admixture from arteriovenous shunts between the portal and pulmonary circulations has been implicated as the pathophysiologic mechanism. Venoarterial shunts in cirrhosis have been found to account for an average of 9.6% of the cardiac output.<sup>7</sup> Increased cardiac output has also been observed by investigators and has been found to be associated with an increased plasma volume, increased stroke volume, normal peripheral blood pressure, and increased hepatic vein wedge pressure. This has been ascribed to decreased peripheral vascular resistance caused by dilation of the peripheral vascular bed and possible arteriove-

Table 1 Cardiac catheterization data

Site	Systolic and diastolic pressures	O <sub>2</sub> saturation
SV C	a = 10 v = 12/10	74
RA	a = 10 v = 8/5	73
RV	0/10	73
PA	0/30/50	71
PAW	a = 10 v = 12/10	88

nous shunting in the extremities. Cardiac hypertrophy has also been found in cirrhotic subjects and this has been thought to involve chiefly the right ventricle. The exact relation of cardiac hypertrophy to increased pulmonary pressures or to increased cardiac output is not known. It has also been suggested that cirrhosis is associated with a specific myocardial disease. Patients with cirrhosis not only have common types of heart disease but are also prone to develop an idiopathic type of heart disease.<sup>7</sup>



More specifically, our patient has the rare association of pulmonary hypertension with cirrhosis of the liver. In previous case reports of cirrhosis and pulmonary hypertension 60% (19 of 32) of the patients had hemodynamic measurements documenting the pulmonary artery hypertension. In the others pulmonary hypertension was suspected on clinical or anatomic grounds. Nineteen of the 32 were subsequently documented to have pulmonary plexiform lesions at autopsy.

In most instances pulmonary hypertension can be readily established by both clinical and invasive studies. The underlying cause is congenital or acquired heart disease, recurrent pulmonary emboli, interstitial pulmonary fibrosis, pulmonary emphysema, or pulmonary veno-occlusive disease is usually apparent. Pulmonary hypertension is then recognized as a feature of the underlying condition. There is however a residuum of cases of pulmonary hypertension for which no cause is evident. Such cases as exemplified by this patient are then diagnosed as having primary pulmonary hypertension.

In a pathologic description of primary pulmonary hypertension Edwards and Edwards point out the difficulty of documenting pulmonary vascular lesions histologically. The lesions may be extremely focal while most of the pulmonary vessels may be normal. As a result the extent of the involvement of the pulmonary vasculature in any one tissue section may appear to be deceptively scant. Of the three pathological patterns that they described the plexogenic type more frequently developed in the cases of hepatic cirrhosis as well as in patients ingesting various anorectic drugs and in those with schistosomiasis.

The hemodynamic disturbances in hepatic cirrhosis have been attributed to idiopathic changes in the pulmonary vessels, expansion of the pulmonary blood volume due to expanded total blood volume, thiamine deficiency, excessive activity of

vasodilator material that is normally inactivated by the liver and emboli from thrombosed portal veins gaining access to the systemic venous system through enlarged collateral veins or to an immunologic mechanism as involved in chronic active hepatitis. However the basic mechanism behind the association of primary pulmonary hypertension and cirrhosis has still to be supported by firm data. Nevertheless the clinical association of these hemodynamic disturbances with cirrhosis is evident and should be brought to the attention of physicians.

### Summary

The association of cirrhosis and primary pulmonary hypertension has been rarely reported. This case report adds to the literature a case documented by liver biopsy and cardiac catheterization. The literature on this subject and potential pathophysiologic mechanisms of association are reviewed.

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## *Histoplasma capsulatum* endocarditis\*

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Nearly 40 years have passed since Humphrey described the initial case of *Histoplasma capsulatum* endocarditis. Only 21 cases of this rare manifestation of histoplasmosis have been reported in the literature<sup>1-11</sup> and only four patients have survived.<sup>1-4</sup> We report a case with aortic valve involvement which was cured by therapy with amphotericin B and aortic valve replacement.

### Case report

Patient W. C., a 72-year-old white male, was in excellent health until April, 1970, when he developed fatigue, nocturnal fevers to 38°C, and a 7 kg weight loss. In September 1970 he was admitted to another hospital where physical examination was normal except for cardiac findings that included an aortic ejection click, a Grade II/VI systolic ejection murmur radiating to the base and apex, and a Grade I/VI high frequency diastolic decrescendo murmur at the left lower sternal border and the second right intercostal space. An echocardiogram revealed variably eccentric aortic valve closure and an aortic thickening of the aortic leaflets in systole and/or diastole depending on transducer angulation. A sleep was not per-

formed. The findings were considered to be consistent with endocarditis and/or a bicuspid aortic valve with mild aortic regurgitation. Although endocarditis was strongly considered, the patient's normal hematocrit, leukocyte count, erythrocyte sedimentation rate, absence of rheumatoid factor, negative blood culture, and spontaneous defervescence prompted the patient's discharge.

Fever recurred in October 1970 and on November 1, 1970 he experienced sudden numbness and weakness in his left arm and leg which spontaneously resolved in one hour. He was admitted on November 6, 1970 for further evaluation.

The patient was a native of Tennessee where he had spent most of his life. There was no history of rheumatic fever or other known valvular heart disease, drug abuse, recent dental work, or diagnostic instrumentation.

Physical examination revealed a thin, chronically ill appearing white male in no acute distress. The blood pressure was 114/40 mm Hg, the pulse 96 per minute and regular, and the temperature 37.5°C orally. The carotid pulse contour was normal and the left ventricular impulse was not displaced. Auscultation revealed normal first and second heart sounds, a Grade II/VI systolic ejection murmur was present with maximal intensity at the second right intercostal space and radiation to the apex and carotid arteries. There was a grade III/VI diastolic decrescendo murmur at the second right intercostal space that extended to S<sub>2</sub> and was heard well at the right and left lower sternal borders. An ejection click was heard by some observers. Except for a palpable spleen tip, the remainder of the physical examination was normal.

The hematocrit was 39%, hemoglobin 12.8 gm/dl, and leukocyte count 4,000/mm<sup>3</sup> with 7% bands, 4% polymorphonuclear leukocytes, and 46% lymphocytes. The erythrocyte sedimentation rate was 33 mm/hr and rheumatoid factor was weakly present at 1:20. A lumbar puncture revealed 88 red blood cells/mm<sup>3</sup>. Urinalysis revealed an occasional red blood cell per high power field. The chest roentgenogram revealed calcified lymph nodes in the right hilum and a normal cardiac silhouette. The electrocardiogram was normal. Repeat echocardiography (Fig. 1) again showed an abnormal aortic valve with variable systolic and/or diastolic leaflet thickening dependent on transducer angulation. Leaflet mobility was

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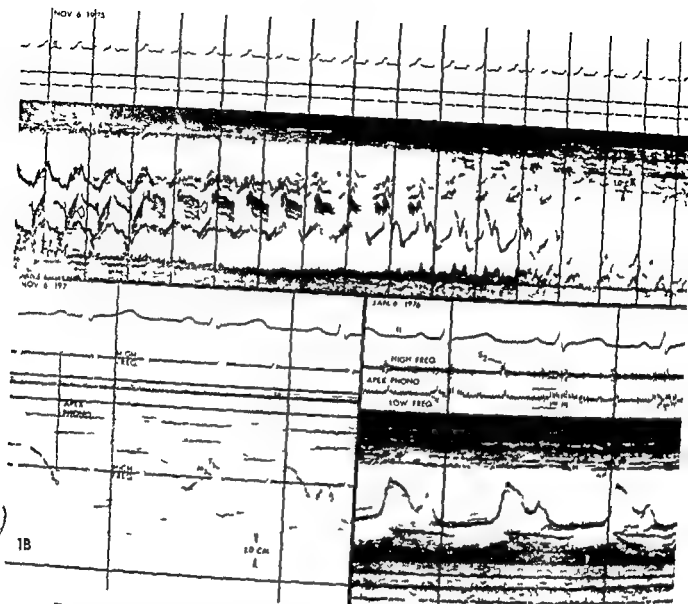


Fig 1 A The initial portion of the echocardiographic sweep shows abnormal systolic thickening (open arrow head) of the non coronary cusp. As the transducer is angled inferiorly, abnormal echoes appear first in the mitral valve (open arrow head) and then in the left ventricular outflow tract (closed arrow head). The left atrial and left ventricular dimensions are normal. B A simultaneous mitral valve echophonocardiogram at rapid paper speed displays the normal QRS-mitral valve closure interval (approximately 50 msec) present on admission and that both component of the first heart sound (M-T<sub>1</sub>) are well preserved. C A simultaneous mitral valve echophonocardiogram recorded just prior to aortic valve replacement shows shortening of the QRS-mitral valve closure interval (approximately 30 msec) and the concomitant appearance of both a presystolic Austin Flint murmur (bracket) and a softening of the mitral component of the first heart sound. Time lines = 10 sec.

normal. The distal echoes were variably dependent on transducer angulation. On sweeping from the aortic mitral valve the distal echoes were not extended into the left ventricular outflow tract although no distal high frequency oscillations were noted. There was distal fluttering of the mitral valve. Left ventricular dimensions and calculated ejection fraction was normal. A QRS-mitral valve closure interval was normal at admission. Multiple cultures of blood, urine and sputum for bacteria and fungi were negative.

Despite persistently negative blood cultures, the suspicion of bacterial endocarditis prompted a two week trial of intravenous penicillin and gentamicin from November 19 to 29, 1973, and a one week trial of vancomycin from December 1 to 8, 1973. Neither course of antibiotics modified the patient's daily hectic fevers to 38°C. On November 27, 1973, complement fixation titers to histoplasma yeast and mycelial phase antigens were 1:64 titers to blastomycosis and coccidioides antigens were 1:16 and 1:8 respectively. Repeat titers on November 29, 1973 simultaneously tested with the serum from November

revealed a rise to 1:256 and 1:512 for histoplasma yeast and mycelia with no change in blastomycetes titer. Skin tests with intermediate strength tuberculin PPD, histoplasmin, coccidioidin and streptokinase-streptodornase were all negative. A liver biopsy on November 23, 1975 revealed noncaseating granulomas containing rare structures consistent with *H. capsulatum*. Culture was unsuccessful because of bacterial overgrowth. Granulomas were also present in bone marrow biopsy material. On December 10, 1975, intravenous amphotericin B was begun and the fever gradually subsided over eight days. On December 15, a bone marrow culture was positive for *H. capsulatum*.

During December 1975 and early January 1976, the patient remained free of symptoms of congestive heart failure but progressive left ventricular enlargement was noted by chest roentgenography and by echocardiography. Left atrial enlargement was noted on echocardiography. An apical precordial Austin Flint murmur developed and the QRS to mitral valve closure interval shortened to a minimum of 30 msec. The calculated ejection fraction remained normal.

On January 7, 1976, he underwent an uneventful replacement of the aortic valve with insertion of a Hancock porcine prosthetic valve. The left atrial pressure at surgery was 24 mm. Hg. The resected aortic valve was tricuspid but markedly deformed by vegetations on each cusp with small perforation in the right and left coronary cusps (Fig. 2). Faint leaflets were not present. Histopathologic examination of the valve revealed organisms consistent with *Histoplasma* (Fig. 3) and culture subsequently grew *H. capsulatum*.

Postoperative recovery was uneventful and a total of 9 gm of intravenous amphotericin B was administered over 20 months. Antibody determinations in September 1976 revealed a *H. capsulatum* yeast titer of 1:16 and a mycelial phase titer of 1:8. At follow up 24 months after valve replacement the patient was asymptomatic, had gained 16 kg and was working as a watchman. The prosthetic valve functioned normally.

## Discussion

The present case is an example of disseminated histoplasmosis presenting as blood culture negative aortic valve endocarditis. The clinical features of the other reported cases of *H. capsulatum* endocarditis are presented in Table I. All cases with the exception of one from rural Canada were inhabitants of the eastern United States or the Ohio-Mississippi Valley region. Splenomegaly was present in 52%, anemia in 75%, normal leukocyte count in 85%, leukopenia in 10%, and leukocytosis in 5%. Microscopic hematoma was present in 50% and the erythrocyte sedimentation rate was elevated in 92%. Blood culture was positive in only one case.<sup>21</sup>

A murmur was present in 68% of the cases. As in the present case, the aortic valve was most frequently the site of infection. The aortic valve alone was involved in 10 cases, the mitral valve

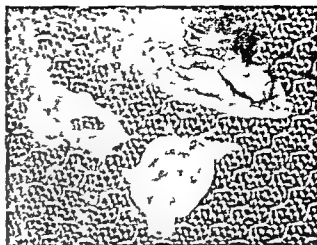


Fig. 2. Aortic valve demonstrating fungal vegetations and multiple leaflet perforation.

alone in five, both aortic and mitral valves were involved in two, the tricuspid valve was involved in two, and the papillary muscle and left ventricle in one. Eleven of 22 cases including the present one did not have underlying valvular disease. When pre-existing heart disease was present it was most frequently rheumatic (six cases) including one case of mitral stenosis associated with an atrial septal defect. Luetic aortic valvulitis with an aortic aneurysm, bicuspid aortic valve, and left atrial myxoma each occurred once. One patient's heart was reported as abnormal but the lesion was not described. No abnormality was noted in the remaining 12 cases.

Cutaneous delayed hypersensitivity reaction to intradermal *H. capsulatum* antigen was of no value in the diagnosis of disseminated histoplasmosis. Of the ten cases including the present one in which response to *H. capsulatum* skin testing was reported, only one had a positive response.

Complement fixation testing provided the first indication of the etiology in the present case. The initial titers were 1:64 to both the yeast and mycelial phases of *H. capsulatum*. The titer rose to 1:256 following a histoplasmin skin test. Although skin testing is known to elevate serologic titers, Kaufman and colleagues<sup>22</sup> have shown that a maximum rise to a titer of only 1:32 occurred with skin testing in previously sensitized individuals. Although possible, it therefore seems unlikely that skin testing resulted in the rising titers demonstrated in the present case. The

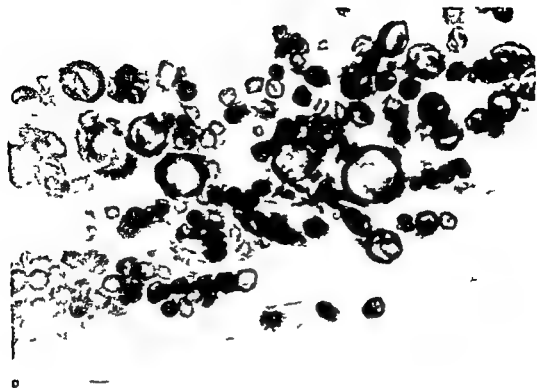


Fig 3 Masses of *H. capsulatum* yeast are present in photomicrograph of section of aortic valve (Methenamine silver stain, original magnification  $\times 60$ )

response to therapy is documented by a gradual fall to a *H. capsulatum* yeast titer of 1:16 and a mycelial titer of 1:8.

Large artery embolization can be an important presenting manifestation of *H. capsulatum* endocarditis. Two of the surviving patients<sup>13, 14</sup> were diagnosed by histologic examination of femoral artery emboli. Our patient presumably suffered a cerebral embolus which prompted his second hospitalization but no peripheral emboli were available for examination. Antemortem diagnosis has also been established by biopsy of the liver,<sup>4</sup> gingiva,<sup>15</sup> and epiglottis.<sup>16</sup> Although biopsy of the liver in the present case revealed organisms consistent with *H. capsulatum*, attempts at culture were unsuccessful because of bacterial contamination. A positive bone marrow culture ultimately established the diagnosis in the present case as it did in one other successfully treated case.<sup>17</sup>

Echocardiography is a useful tool in the detection of fungal endocarditis of the aortic and mitral valves and in the evaluation of hemodynamic severity. The abnormal echoes from the aortic valve in the present case are typical of the valvular vegetations described both in fungal

and bacterial endocarditis. No high frequency diastolic oscillations of the echoes were seen but they did extend into the left ventricular outflow tract (Fig 1). At operation flail leaflets were not seen and these echoes undoubtedly reflected the vegetations that extended below the leaflets into the left ventricular outflow tract.

Presystolic closure of the mitral valve in the absence of a prolonged PR interval is a reliable echocardiographic sign of acute aortic regurgitation with a rising left ventricular diastolic pressure. In this patient the interval was initially normal but progressively shortened reaching a low of 30 msec prior to surgery. This interval change occurred in the setting of an unchanged PR interval (160 msec) and correlated well with the appearance of an apical Austin Flint rumble. Although mitral valve closure never preceded the onset of the QRS complex, the interval of 30 msec is well below the range of normal reported by Waider and Craige<sup>18</sup> together with the change in heart size this reflected increasingly severe aortic regurgitation. The decision to replace the aortic valve in this patient was supported by recent studies emphasizing the importance of early valve replacement when heart failure super-

Table 1 Histoplasma endocarditis

Reference	Case	Date	Age	Sex	Cardiac murmur	Time to diagnosis (months)	Diagnostic methods	Valve involved	Previous cardiac disease	Outcome
1	1	1939	17	M	—	70	NA	LV papillary muscle LV anterior surface	None	Death
2	2	1939	53	M	—	NA	Necropsy	Aortic	None	Death
3	3	1938	34	M	+	7.5	Necropsy	Aortic	Syphilitic aortic valvulitis & aortitis	Death
4	4	1912	47	M	+	■	Liver bx	Aortic Mitral	RHD	Death
5	5	1944	59	M	—	9	Necropsy	Tricuspid	None	Death
6	■	1945	55	F	+	4	Necropsy	Mitral	MS present	Death
7	7	—	32	F	+	13	NA	Aortic	Not described	Death
8	8	1949	64	M	—	34	Gingival	Tricuspid	None	Death
9	9	—	■	M	+	8	NA	Aortic	None	Death
10	10	1954	44	M	+	10	Necropsy	Aortic	Bicuspid aortic valve	Death
11	11	1955	50	M	—	31	Necropsy	Aortic	None	Death
12	12	1955	35	M	+	21	Necropsy	Aortic	None	Death
13	13	1956	50	M	+	3	Pharyngeal bx	Mitral	RHD	Death
14	14	1957	37	F	+	6	Necropsy	Aortic	RHD	Death
15	15	1959	27	F	+	10	Femoral embolism	Mitral	None	Cured with 4.2 grams of amphotericin B
16	16	1963	50	M	+	9	Necropsy	Mitral	ASD RHD	Death
17	17	1963	61	M	—	NA	Femoral embolism	NA	None	Cured with 40 grams amphotericin B
18	18	1965	3	M	+	2	Necropsy	Mitral	RHD	Death
19	19	1965	59	M	—	4	Necropsy	Aortic	None	Death
20	20	1968	45	M	+	2	Bx of epiglottis	Aortic Mitral	None	Cured with 1.49 grams of amphotericin B
21	21	1977	48	F	+	7	Echocardiography Complement fixation serology		Atrial myxoma	Cured with 2.1 gm of amphotericin B & atrial myxoma resection
Present case	22	1975	22	M	+	8	Bone marrow bx	Aortic	None	Cured with 2.0 grams of amphotericin B & aortic valve replacement

Abbreviations: NA = not available; LV = left ventricle; RHD = rheumatic heart disease; MS = mitral stenosis; bx = biopsy; M = male; F = female; + = present; — = absent.

venous during the course of bacterial<sup>1,2</sup> or fungal<sup>3</sup> endocarditis.

The optimal dosage of amphotericin B for therapy in disseminated fungal infections has not been precisely defined. Two grams of amphotericin B have been curative in disseminated histoplasmosis.<sup>1,2</sup> *H. capsulatum* endocarditis has been successfully treated medically with 4.2 gm,<sup>15</sup> 40 gm,<sup>16</sup> 1.49 gm,<sup>20</sup> and 2.1 gm<sup>21</sup> of amphotericin B. Although our patient showed a favorable clinical response to the administration of 0.72 gm amphotericin B over four weeks, valve replacement was necessitated by hemodynamic deterio-

ration and viable *H. capsulatum* were demonstrated in the valve removed at surgery. Thus apparent failure of medical therapy could have resulted from poor penetration of amphotericin B into the fungal vegetations,<sup>22</sup> despite presumably adequate serum antibiotic levels.

*H. capsulatum* endocarditis should be managed similarly to other forms of endocarditis. Since cases have been successfully treated medically,<sup>1,2,23</sup> valvular replacement is probably only indicated when there is hemodynamic deterioration, recurrent embolization, or failure of medical therapy alone.

## Summary

Endocarditis is a rare manifestation of disseminated *Histoplasma capsulatum* infection. A 22 year old man presented with a seven month history of fever weight loss and progressive aortic insufficiency. The diagnosis of *H. capsulatum* was suggested by a diagnostic rise in complement fixation titers and positive echocardiographic findings. The diagnosis was confirmed prior to surgery by positive bone marrow culture. Progressive congestive heart failure necessitated replacement of the aortic valve which subsequently grew *H. capsulatum*. In this case a combination of amphotericin B therapy and valve replacement was curative.

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# Clinical pathologic conference

## Primary pulmonary hypertension

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**CLINICAL SUMMARY** This 60 year old hypertensive non diabetic woman had a 3 year history of dyspnea on exertion orthopnea and pedal edema treated with digitalis and diuretics She was first hospitalized in May 1976 for surgical correction of an incarcerated abdominal hernia At that time she was noted to have a prominent mitral regurgitation murmur with cardiomegaly and compensated congestive heart failure There was no history of acute rheumatic fever or myocardial infarction

The patient was lost to follow up for several months during which time she ceased taking her diuretic She developed progressive pedal edema dyspnea on exertion and paroxysmal nocturnal dyspnea She had occasional episodes of precordial pressing chest pain radiating to the arms associated with nausea and diaphoresis and never lasting more than 5 to 15 minutes The pain was not pleuritic or positional and was relieved by nitroglycerin When her symptoms worsened she sought medical attention and she was admitted to the hospital

On physical examination the patient was obese dyspneic and cyanotic in obvious respiratory distress The pulse was regular and 108/minute respirations were 40/minute and the blood pressure was 140 mm Hg systolic by palpation She was afebrile There was jugular venous distension at 30 degrees There were mild hypertensive changes in the fundi The chest was dull to percussion one third of the way up on the right

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and one fourth of the way up on the left On auscultation there were decreased breath sounds at both bases with a bronchovesicular quality and no rales or ronchi The point of maximal cardiac impulse was in the fifth intercostal space in the anterior axillary line There was a Grade V/VI holosystolic apical murmur with a thrill radiating to the axilla No diastolic murmur or gallops were heard S<sub>1</sub> and S<sub>2</sub> sounds were diminished The abdomen had a fluid wave shifting dullness and bulging flanks The liver edge was palpated four finger breadths below the right costal margin The extremities revealed 3+ pitting edema to the knees and cyanosis The remainder of the physical examination was unremarkable

The patient had a hematocrit of 54.3 volumes per cent and a hemoglobin of 18 gm/100 ml The white blood count was normal The electrolytes were sodium 147 mEq/L potassium 4.7 mEq/L chloride 109 mEq/L and CO<sub>2</sub> 14 mEq/L The blood glucose was 238 mg per cent the blood urea nitrogen 23 mg per cent and the creatinine 1.2 mg per cent Total bilirubin was 2.1 mg per cent and direct bilirubin was 1.0 mg per cent The prothrombin time was slightly elevated The serum glutamic oxaloacetic transaminase was 54 units the lactic dehydrogenase was 361 units and the creatine phosphokinase was normal Urinalysis showed 3+ protein Arterial blood gases on room air revealed a pH of 7.31 an oxygen partial pressure (PO<sub>2</sub>) of 24.5 mm Hg and an oxygen saturation of 67% The electrocardiogram showed normal sinus rhythm PR interval 0.12 QRS interval 0.09 axis +150 degrees P mitrale and bigeminy The chest x ray revealed bilateral pleural effusions and cardiomegaly An echocardiogram showed right ventricular hypertrophy



concentric left ventricular hypertrophy with a good ejection fraction and normal left atrial size

The patient was intubated and treated with 70% oxygen. The arterial blood gases improved and the patient looked and felt better. However she required a constant dopamine drip infusion to maintain blood pressure at 100 mm Hg. Attempts to insert a Swan Ganz catheter were unsuccessful and resulted in trauma to the left brachial artery with subsequent thrombosis of the radial artery. The vessel was repaired under local anesthesia with resection of a small portion of brachial artery removal of thrombus and end to end anastomosis. Good blood flow was established in the extremity. She was given 5000 units of heparin. She developed upper gastrointestinal bleeding and bleeding from the endotracheal tube but this stabilized spontaneously.

Approximately 20 hours after admission the patient had a respiratory arrest and an anoxic seizure. Attempts at resuscitation were initially successful; however she died several hours later.

#### Clinical discussion

DR JOSEPH REICHEL. This case defies concise analysis. The data which must be reconciled are the mitral regurgitation murmur unexplained prior shock cardiomegaly and P mitrale without left atrial enlargement polycythemia hypoxemia right ventricular hypertrophy and the absence of pulmonary congestion.

I will take the position that this patient had right ventricular hypertrophy and pulmonary hypertension. The data which substantiate this are as follows. In May 1976 there was a wandering atrial pacemaker at a rate of 68 and an S, Q, T3 pattern with ST-T wave depression in Leads II, III, aV, and V to V. In March 1977 the electrical axis was +150 degrees with R greater than S in Leads V and V. There was a strain pattern with an incomplete right bundle branch block. The echocardiogram showed right ventricular hypertrophy concentric hypertrophy of the left ventricle with a good ejection fraction and normal left atrial size.

In approaching the causes of pulmonary hypertension it is necessary to start at the aortic valve and work back to the lung and the pulmonary vasculature. We will have to consider rheumatic

and calcific aortic stenosis as well as idiopathic hypertrophic subaortic stenosis. We shall have to include in our discussion dilatation of the mitral ring due to left ventricular failure and hypertension. Occult mitral stenosis and diseases which mimic occult mitral stenosis such as atrial myxoma and atrial thrombus will enter our differential. The question of the patient's mitral regurgitation whether due to cardiomyopathy rheumatic fever papillary muscle rupture or dysfunction or rupture of chordae tendineae will have to be examined. Transmission of high pressure to the right ventricle through a ventricular septal defect possibly due to myocardial infarction and an aneurysm of the sinus of Valsalva will have to be mentioned. It is unlikely that this clinical picture is produced by an atrial septal defect. Pulmonary venoocclusive disease primary pulmonary hypertension and recurrent pulmonary emboli also have to be considered. At this point I wish to mention primary pulmonary diseases as a cause of polycythemia and right ventricular hypertrophy only to dismiss this group of conditions. There is no history of cough, sputum production, tuberculosis, occupational exposure or other prior pulmonary disease. In addition we will mention only to exclude the remote possibility that this patient who died with abdominal distention and a guaiac positive nasogastric aspirate had mesenteric vascular disease or rupture of an aortic aneurysm.

Aortic stenosis is an unlikely diagnosis because of the brisk carotid pulses the absence of a diamond shaped cardiac murmur and the presence of right ventricular hypertrophy. Although the murmur of aortic stenosis in an elderly person may occasionally radiate to the apex axillary radiation with a thrill is extremely unlikely. Idiopathic hypertrophic subaortic stenosis can probably be ruled out because of the negative echocardiogram in 1977 the absence of severe asymmetrical left ventricular hypertrophy and the lack of a Q wave in Leads II, III, aV, and the left precordium. Furthermore this fails to explain the presence of right axis deviation and right ventricular hypertrophy. Cardiomyopathy rheumatic or cause severe mitral regurgitation however, with no history of recurrent arrhythmias and with the presence of severe right axis deviation this diagnosis is low on our differential list.

We must give more thought to the possibility of silent mitral stenosis with extreme pulmonary vascular obstruction. This condition is characterized by dyspnea orthopnea and syncope right ventricular failure may be present. Of importance the pulmonary artery is usually dilated and there is pruning of peripheral vessels which was not observed in our case. Although there may be no history of rheumatic fever a right ventricular heave an opening snap of the mitral valve an increase in intensity of the first sound and the pulmonary component of the second heart sound and an increase in size of the left atrium pulmonary artery and right ventricle are commonly seen. P mitrale may or may not be observed and atrial fibrillation is almost invariably present. Because of the regular rhythm and normal sized left atrium I tend to exclude silent mitral stenosis.

A more likely diagnosis especially because this is a CPC is a cardiac tumor specifically an atrial myxoma. Atrial myxomas comprise 30 to 50% of cardiac tumors. They are more common in women than men in a 3 to 1 ratio and 75% are in the left atrium. Valvular obstruction may simulate mitral or tricuspid stenosis. The murmur of mitral regurgitation or tricuspid regurgitation also has been described. Right atrial myxomas may cause or simulate pulmonary hypertension and may cause increased hematocrit. Clubbing and cyanosis with a variable right to left shunt associated with a change in position may occur if there is a patent foramen ovale or an atrial septal defect. Systemic effects including fever leukocytosis weight loss elevation of the sedimentation rate and hyperglobulinemia are commonly seen in atrial myxoma and were not present in our patient. The absence of abnormal findings in the left atrial echocardiogram also mitigate against atrial myxoma however we cannot rule out a right atrial myxoma projecting into the left atrium through an atrial septal defect or multiple atrial myxomata. In a review of left atrial myxoma 28 of 40 patients had pulmonary hypertension 22 of 40 had a systolic murmur and 10 had pulmonary embolism.

One entity which has a clinical appearance similar to atrial myxoma is atrial thrombus. Here sudden death may occur usually in the presence of mitral stenosis and atrial fibrillation. There is usually severe pulmonary congestion and past or

recent peripheral emboli. The symptoms are eased by leaning forward and there may be changing murmurs and periodic numbness of the hand and feet. Patients may have an accelerated downhill course. The negative echocardiogram and the absence of atrial fibrillation changing murmur and episodes of numbness are against the diagnosis.

Calcification of the mitral ring may elevate the valve leaflets stretch the chordae tendineae and produce mitral regurgitation. The picture of progressive pulmonary congestion and right ventricular failure over 4 to 8 years may be seen however in the absence of calcification on x ray we cannot make this diagnosis in our patient.

In distinguishing severe from mild mitral regurgitation the following factors must be considered. In severe mitral regurgitation there is a palpable left ventricular heave a loud S<sub>2</sub> sound evidence of left atrial abnormality a wide split S<sub>2</sub> sound and usually a history of rheumatic fever. In contrast in mild mitral regurgitation there is no increase of left ventricular activity no sounds are heard in diastole there is normal left atrial size and no symptoms of congestive heart failure or history of rheumatic fever are present.

We should give some consideration to the question of mitral regurgitation due to coronary artery disease. Rupture of a papillary muscle or chordae tendineae attachment occurs in 1% of myocardial infarctions whereas papillary muscle dysfunction occurs in 20%. Rupture of the body of a papillary muscle causes rapid pulmonary edema shock and death. In contrast rupture of a single head of a papillary muscle produces a sudden catastrophe in a patient recovering uneventfully from myocardial infarction. There may be a Grade 3 or 4 murmur radiating to the axilla with a thrill an S<sub>3</sub> and S<sub>4</sub> gallop and a small left atrium. Usually the electrocardiogram shows a myocardial infarction. The pulmonary artery pressure and pulmonary vascular resistance are high and the prognosis is very poor. Fewer than 20% of patients survive two weeks. Without surgery there is usually death from congestive heart failure within a short time.

Let us consider papillary muscle dysfunction. This entity may occur as a result of distortion of the normal spatial relations between the papillary muscle the valve leaflets and the ventricle. Dilatation of the ventricle idiopathic hyper



fig 1 The opened right heart reveals marked ventricular hypertrophy with prominence of the papillary muscle and the tricuspid valve ring. The ventricular wall measures up to 1 cm. The atrium is dilated. Focal fibroelastosis of the endocardium is visible as patches on the ventricular surface. The septal leaflets are minimally thickened and the septum shows an irregular perforation (arrow) which probably represents healed infective endocarditis. The roughened atrial endocardium shows this lesion indicative of valvular insufficiency, cannot be appreciated from this view.

trophic subaortic stenosis the click murmur syndrome fibroelastosis and carcinoid tumor may cause this dilatation. There may be intrinsic abnormalities of the papillary muscles due to coronary atherosclerosis, abscess or vasculitis. In addition there may be functional abnormalities of the papillary muscle. Asynchrony between contraction of the papillary muscle and left ventricular contraction may cause papillary muscle dysfunction. The symptoms are generally those of coronary artery disease. There may be chest pain and pulmonary edema with varying degrees of mitral regurgitation. There is usually a soft high pitched musical holosystolic Grade I-II murmur and there may be a click late systolic murmur syndrome. There is often evidence of myocardial infarction and ST depression in the lateral precordial leads. Ventricular function is frequently bad. Because our patient had a rather loud murmur with a thrill and because of the absence of electrocardiographic evidence of myocardial infarction it is unlikely that our patient's problems were caused by papillary muscle dysfunction.

Mitral regurgitation due to rupture of the chordae tendineae may be due to subacute bacterial endocarditis or to rheumatic heart disease, congenital coronary or aortic disease or to

rupture. In rheumatic heart disease the condition worsening may occur and the syndrome may be associated with atrial fibrillation or dilatation of the left atrium. There is often significant aortic and mitral regurgitation. Isolated rupture of the chordae tendineae commonly occurs in males aged 40 to 60. There is no history of rheumatic fever and there may be sudden dyspnea and pulmonary edema. There is a sudden loud harsh systolic murmur. The left atrium is normal sized and there is no cardiomegaly. Rhythm is sinus despite the presence of severe mitral regurgitation and there is usually a prominent S<sub>1</sub> and S<sub>2</sub> sound with a brief diastolic murmur. The second pulmonary sound is widely split and there may be minimal symptoms including episodic dyspnea and chest pain. The echocardiogram usually shows preservation of ventricular contractility. Because the murmur of spontaneous rupture of the chordae tendineae usually radiates from the apex to the aortic area and because we cannot explain right ventricular hypertrophy on this basis I rule out this diagnosis. In one review of 23 patients with rupture of a head of the papillary muscle or of chordae tendineae 22 of 23 patients had sinus rhythm and a harsh systolic murmur. In five cases there was radiation to the axilla. In all cases the chest x-ray showed pulmonary edema which further rules against the diagnosis in our case.

We must also consider rupture of the ventricular septum which can occur a few hours to six weeks after myocardial infarction producing dyspnea and shock. There is biventricular failure and a loud holosystolic murmur in the third, fourth and fifth interspace at the left sternal border. In one third of cases the murmur radiates to the apex. The left to right shunt may produce pulmonary hypertension however most individuals have evidence of myocardial infarction and less than 15% of patients survive two months.

Even less likely would be an aneurysm of the sinus of Valsalva which usually produces a continuous murmur over the left precordium in the third to the fourth interspace. Right axis deviation is usually not seen.

Much more consideration should be given to the possibility of primary pulmonary hypertension. In one review of 23 patients the disease was more common in females in a ratio of five to one. The age of the patients ranged between 11 and 56 years. Syncope which has been associated

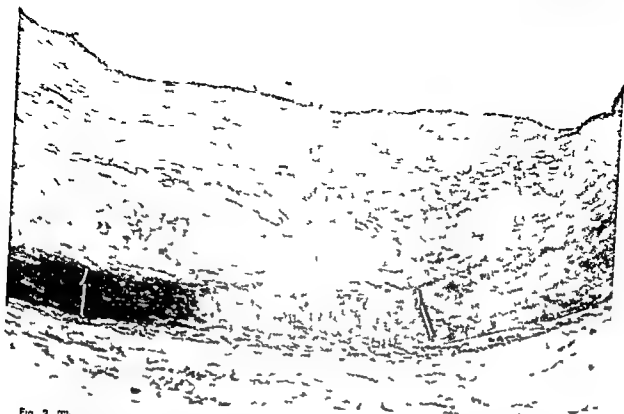


Fig 2 This section of main pulmonary artery reveals striking intimal thickening (the region above the arrow) with changes typical of athero-sclerosis including fibro- and lipid deposition (the intimal clefts represent dissolved cholesterol). The underlying media (labeled bla F) has compressed elastic lamellae and is focally thinned. This degree of pulmonary atherosclerosis is rare except in cases of severe pulmonary hypertension (Verhoeff van Gieson elastic tissue stain original magnification  $\times 8$ )

this entity was only seen in six patients. Seven patients had Raynaud's disease and three patients had arthritis. A systolic murmur which may be due to tricuspid regurgitation was seen in 10 patients and 12 patients had thromboemboli. The etiology of this entity is not known. Suggested causes include congenital lesions collagen vascular diseases multiple small emboli vasospasm or familial tendency. Wagenvoort and Wagenvoort examined material from 106 patients in whom the diagnosis of primary pulmonary hypertension had been made. In 31 patients there was evidence of organizing thrombi intimal fibrosis and intra arterial septa—suggesting thromboembolic disease. A small number of patients had veno occlusive disease sarcoidosis chronic obstructive pulmonary disease and schistosomiasis. In 110 cases there was medial hypertrophy intimal fibrosis arteritis and morphologic changes of pulmonary hypertension identical to those seen in individuals with congenital

heart disease. The major argument against primary pulmonary hypertension in this case is the patient's age. Most patients with this entity are younger.

We must briefly consider pulmonary veno occlusive disease in which there is severe venous intimal fibrosis and capillary dilatation. Arterial changes may be similar to those seen in primary pulmonary hypertension and in fact this disease is considered by some to be a variant of this condition. In all instances however the x-ray shows pulmonary edema which our patient did not have.

I think it most likely that our patient had recurrent multiple pulmonary emboli. The electrocardiogram in acute pulmonary embolism shows an S Q T<sub>3</sub> pattern in 12% of patients a right bundle branch block in 9% of patients and right axis deviation in 7% of patients.<sup>21</sup> These changes are due to pulmonary hypertension and return to normal when pulmonary pressures drop.

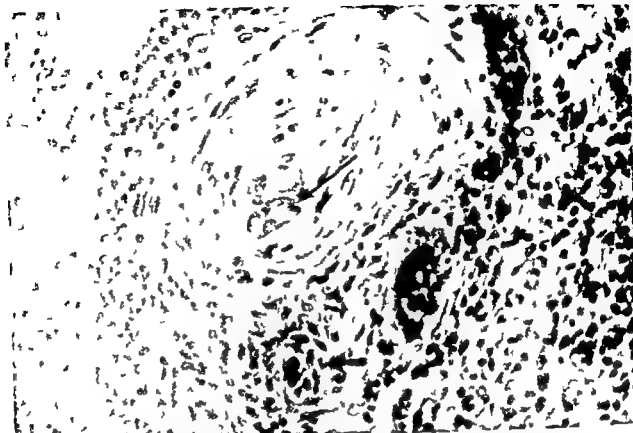


Fig 3 This small muscular pulmonary artery is almost completely occluded by concentric intimal fibrosis. The vessel lumen is filled with a recent fibrin thrombus (thin arrow) surrounding the vessel and presumably attached to it is a portion of a plexiform lesion (thick arrow) (Hematoxylin and eosin, original magnification  $\times 400$ ).

The IDH and bilirubin are often elevated as demonstrated by our patient. Chest x ray abnormalities in acute pulmonary embolism are very common but non-specific. One may see consolidation, pleural effusions, prominence of the pulmonary artery segments, atelectasis, and focal oligemia. Hypoxemia in pulmonary embolism is commonly seen and is thought to be due to a shift of distribution of perfusion to areas of low ventilation/perfusion ratio. In one study of 12 individuals from 8000 consecutive autopsies where congestive heart failure was found without any other cause, all patients had dyspnea, one patient had syncope, 10 of the patients were cyanotic, five had tricuspid murmurs, all of the patients had normal sinus rhythm, and 11 patients had right ventricular hypertrophy. All of the patients showed organized emboli in the tertiary arteries of both lungs, which were often indistinguishable from in situ thrombi.<sup>1</sup> Half of the patients had thrombi in the venous system and a small percentage had intra-arterial thrombi.

It is therefore my impression that our patient had recurrent multiple pulmonary emboli in chronic cor pulmonale. There may be tricuspid regurgitation due to pulmonary hypertension mimicking mitral insufficiency or there may in fact be mitral regurgitation due either to sile rhumatic heart disease, ruptured chordae tendinae, or hemodynamic causes. Finally, left ventricular hypertrophy secondary to hypertensive cardiovascular disease, chronic passive congestion of the viscera, and gastrointestinal hemorrhage due to stress ulcers will probably be found.

#### Autopsy findings

DR STEPHEN M. FACTOR: Dr Reichel's concise and superb discussion of this difficult case mirrors many of the diagnoses which we pathologists must consider when dealing with pulmonary hypertension and co-pulmonary. In particular, we must differentiate three conditions which may have identical clinical features but have distinct histopathological changes.

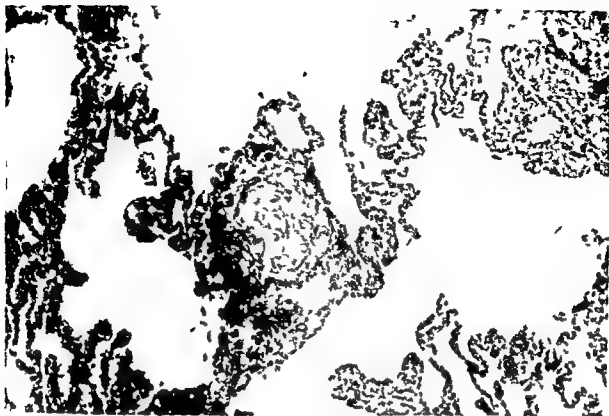


Fig 4 This low power view of the lung shows a muscular pulmonary artery with a narrowed lumen secondary to medial hypertrophy and intimal fibrosis. The pulmonary parenchyma with the exception of mild focal septal thickening is unremarkable (Hematoxylin and eosin original magnification  $\times 78$ )

chronic recurrent pulmonary thromboembolism (2) pulmonary veno occlusive disease and (3) plexogenic pulmonary arteriopathy. It has been stated<sup>3</sup> that these diseases may only be distinguished by lung biopsy or necropsy. Having the advantage of the latter, I hope to demonstrate that we can make a specific diagnosis in this case.

The postmortem examination revealed evidence of marked right sided heart failure with bilateral pleural effusions, ascites and visceral congestion. The heart weighed 450 gm and had striking right atrial and right ventricular hypertrophy and dilatation (Fig 1). Focal endocardial fibroelastotic plaques were noted in the right ventricle, probably secondary to turbulent flow or mural thrombosis. The tricuspid valve ring was dilated, most likely accounting for the insufficiency murmur. However, we also noted a small perforation in the septal leaflet of the tricuspid valve with a jet lesion on the atrial wall above it. This perforation was possibly caused by silent endocarditis which subsequently healed. Its

contribution to the tricuspid insufficiency could not be determined.

The three other valves were morphologically normal and there was no evidence of associated stenosis or insufficiency. The left ventricular cavity was small due to concentric myocardial hypertrophy secondary to hypertension. There was a subaortic muscular bulge with some endocardial thickening; however, there was inadequate evidence of a friction lesion due to systolic anterior motion of the mitral valve. Additionally, though we found rare disorganized muscle fibers in the ventricular septum (whorls), they were few enough in number for us to rule out idiopathic hypertrophic subaortic stenosis as the etiology of these changes.

The pulmonary artery had severe intimal fibrosis as well as obvious atherosclerotic plaques consistent with pulmonary hypertension (Fig 2). These alterations could be seen grossly in many of the distal branches which were dilated and tortuous out to the pleural surface. With the exception of the pulmonary vessels, the lungs



Fig 5 A plexiform lesion arising from a medium sized pulmonary artery. Note its thin wall and lumen composed of small and small vascular channel (arrow) devoid of elastic tissue (Verhoeff van Gieson elastic tissue stain magnification  $\times 200$ )

were not remarkable on gross examination and their weight was only slightly increased above the normal range

Histologically three lesions were observed in large numbers of small and medium sized muscular arteries. Concentric intimal fibrosis (Fig 3) of varying degrees was present as was isolated medial hypertrophy (Fig 4). If these two alterations were all that we found we would have difficulty in making a definitive diagnosis because these changes may be seen in all forms of pulmonary hypertension. However the presence of angiomatoid or plexiform lesions which we saw frequently provided support for our diagnosis. These lesions (Figs 5 and 6) which represent localized expansions or aneurysmal dilations of the muscular pulmonary arteries with pronounced endothelial proliferation in a plexiform pattern are characteristically found in primary pulmonary hypertension. Although they may also be seen in long standing left to right cardiac shunt or in rare cases of hepatic cirrhosis

in the absence of these conditions they are virtually diagnostic of the disease now known as primary plexogenic arteriopathy.<sup>1</sup>

For the sake of completeness the only diagnostic feature that we did not observe in this case which has been reported in plexogenic pulmonary arteriopathy was necrotizing arteritis. We did note rare fibrin deposits in vessel walls however true necrosis was absent. We also saw occasional organized and recent thromboemboli but these were most often associated with the plexogenic lesions.

The presence of thromboemboli raises the question whether all of the lesions that we observed could be secondary to recurrent embolization. This is not an unimportant consideration since recurrent emboli can lead to severe pulmonary hypertension. In the past some pathologists thought that this was the cause of plexogenic pulmonary arteriopathy. However the histopathological changes are different from those in today's case. In most cases of recurrent throm

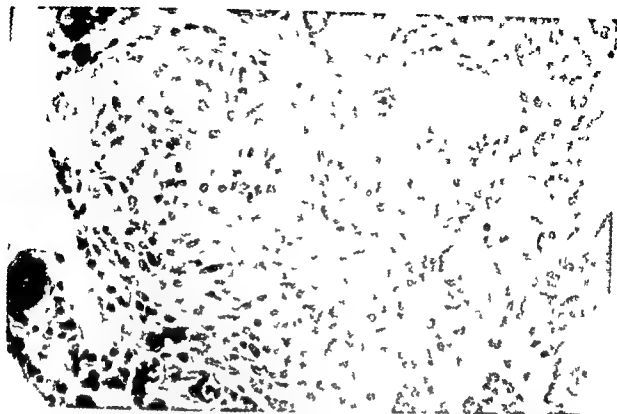


Fig. 6 This high magnification of a plexiform or angiomatous lesion shows many proliferated endothelial cells in the lesion which are not associated with red blood cells. (H. & E. stain and 600 original magnification  $\times 50$ )

the lesion is made up of multiple small channels. There are many proliferated endothelial cells in the lesion which are not associated with red blood cells. (H. & E. stain and 600 original magnification  $\times 50$ )

boemboli leading to pulmonary hypertension the lesions are also found in the muscular branches of the pulmonary arterial tree. However characteristically the emboli produce eccentric intimal fibrosis, fibrous septa, and recanalized thrombi occluding the vessels. Plexogenic lesions and necrotizing arteritis do not occur. Thus the occasional thromboembolus in our case most likely represents a secondary event occurring in a terminally ill patient.

Regarding the third condition which may produce primary pulmonary hypertension—venous occlusive disease—both the clinical features and the histology in this case allow us to rule out this diagnosis. This rare disease generally affects children and young adults. It primarily involves pulmonary veins and venules with intimal fibrous tissue proliferation producing vascular obstruction. As a consequence of venous obstruction there is distention and tortuosity of capillaries with intraparenchymal hemorrhage and hemosiderin deposition. As a secondary

event there may be arterial fibrosis and medial hypertrophy, but arteritis and plexiform lesions are absent.

Therefore we are confident that today's case represents an example of plexogenic pulmonary arteriopathy. The marked pulmonary hypertension led to the development of massive right ventricular hypertrophy and cor pulmonale. The dilatation of the tricuspid valve ring accounted for the insufficiency murmur, although there may have been a contribution from the perforation of the tricuspid valve leaflet. The cause of death was ultimately a result of right-sided congestive heart failure.

One final word about the etiology of plexogenic pulmonary arteriopathy. Despite extensive speculation the etiology remains unknown. Most recent studies suggest a primary role for increased pulmonary vasoconstriction or spasm. An association of plexogenic pulmonary arteriopathy with Raynaud's phenomenon supports this speculation. In the present case we carefully examined



many systemic vessels in the hope that we might find medial hypertrophy suggestive of spasm. However, no significant abnormalities were noted. Therefore, as in most such cases, we are left without a specific cause for the unusual alterations in the pulmonary vasculature.

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## A unified classification for tricuspid atresia\*

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Recent description of physiologic correction of tricuspid atresia by innovative surgical techniques by Fontan and Brude<sup>1</sup> and by Kreuzer and colleagues prompted reexamination of the lesion. A symposium on tricuspid atresia held during the 46th Annual Meeting of the American Academy of Pediatrics Scientific Sessions of Section on Cardiology in November 1977 was the result of one such attempt. After discussion of the surgical aspects of this complex anomaly the need for a more suitable classification became apparent. Tricuspid atresia has been classified on the basis of tricuspid valve morphology, roentgenographic appearance of pulmonary vascular markings and associated cardiac defects. None of the existing classifications is entirely satisfactory. The purpose of this paper is to review the previously proposed classifications and to utilize selected features in a new comprehensive yet unified approach that offers greater clinical utility.

### 1 Classification based on morphology of the atrial tricuspid valve

Tricuspid atresia is characterized by congenital agenesis or absence of the morphologic tricuspid valve. By far the most common anatomic pattern is the muscular variety—a dimple or a localized fibrous thickening may be seen in the floor of the right atrium at the usual site of the tricuspid valve. No valvar material can be identified either by gross or microscopic examination. Occasional

cases have been reported in which minute valvular cusps may be present but are completely fused—this has been called the valvular type. The atrioventricular portion of the membranous septum forms the floor of the right atrium at the expected location of the tricuspid valve in the membranous type of tricuspid atresia. This anomaly has been described with and without juxtaposition of the atrial appendages. In the Ebstein's type three tricuspid valve leaflets are plastered onto the right ventricular wall.<sup>11</sup> The leaflets are fused; there is no valve orifice. The resultant shelf of tissue separates the atrial sized right ventricle from the right ventricular outflow tract. The final form occurs with common atrioventricular canal in which a leaflet of the common atrioventricular valve completely seals off the only entrance into the right ventricle.

The first formal classification of tricuspid atresia based on the morphology of the tricuspid valve was proposed by Van Praagh and associates in 1971: (a) muscular type, (b) fibrous (membranous) type and (c) Ebstein's type. This classification was later modified by him and by Weinberg as shown in Table I. The muscular type constituted 84% of Van Praagh and associates' and 76% of Weinberg's cases. The membranous type was observed in 8% (three out of 38) of Van Praagh and associates' cases and in 12% (four out of 33) of Weinberg's cases, but in only 15% (one out of 83) of Anderson and colleagues' cases.<sup>11</sup> The valvular type comprised 5% (four of 83) and 6% (two out of 33) respectively in the cases of Anderson and co-workers<sup>11</sup> and in Weinberg's cases. The Ebstein's type was found in 8% (three out of 38) of Van Praagh and associates' cases and 6% (two out of 33) of Weinberg's cases, differing from the frequency rates in our series (one out of 38, 2.5%) and in Anderson's series<sup>11</sup>

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**Table I** Classification of tricuspid atresia based on the morphology of the tricuspid valve\*

- 1 Muscular type
- 2 Membranous type
- 3 Valvular type
- 4 Ebstein type
- 5 Atrioventricular canal type

Modified from Van Praagh et al., Van Praagh, and Weinberg

**Table II** Classification of tricuspid atresia based on x-ray appearance of pulmonary vascular markings\*

- A Decreased pulmonary vascular markings
- B Normal or increased pulmonary vascular markings
  - 1 Initially normal or increased, latter changing to decreased pulmonary vascular markings

Adapted from Astley et al. and Dick et al.

(two out of 83.2%). Only a few cases of this type have been recorded in the literature<sup>1,11,12</sup> attesting to the rarity of this lesion. The atrioventricular canal type was mentioned briefly by Van Praagh. This type was not found in the original series reported by him, nor in the pathologic studies reported by Anderson and co-workers<sup>3</sup> and by Weinberg, and must be very rare.

This classification may be useful for pathologic characterization, but it has limited clinical value. Hemodynamically and angiographically the muscular, membranous, and valvular types are indistinguishable from each other. Surgical considerations for these three types are the same. The Ebstein's type may not belong to the tricuspid atresia group, both on the basis of pathologic appearance and embryologic origin.<sup>14</sup> It also is hemodynamically indistinguishable from classic cases of tricuspid atresia, but angiographically it can be distinguished. A right atrial angiogram shows the left border of the right atrial shadow to be displaced more to the left than is usual in tricuspid atresia. The most important reason why this type should be differentiated from other types of tricuspid atresia is because of the surgical implication. Whereas a palliative procedure or Fontan type of operation would be considered for other types of tricuspid atresia, excision of the imperforate Ebstein's tricuspid valve with prosthetic valve replacement is presently the procedure of choice in this type of

**Table III** Classification of tricuspid atresia based on associated anatomic defects\*

- Type I Normally related great arteries
  - a Pulmonary atresia and intact ventricular septum
  - b Pulmonary hypoplasia and small ventricular septal defect
  - c No pulmonary hypoplasia and large ventricular septal defect
- Type II D-transposition of the great arteries
  - a Pulmonary atresia with ventricular septal defect
  - b Pulmonary stenosis with ventricular septal defect
  - c Normal or large pulmonary artery with ventricular septal defect
- Type III L-transposition of the great arteries
  - a Pulmonary or subpulmonary stenosis
  - b Subaortic stenosis

Modified from Kuhne, Edwards and Burchell, Keith et al., Diehl et al., and Rothenb.

anomaly.<sup>13,14</sup> The atrioventricular canal type is extremely rare. In summary, the important anatomic types of tricuspid atresia (with the exception of the Ebstein's type) can not be clinically distinguished from each other, nor is such identification clinically useful.

## II Classification based on the roentgenographic appearance of pulmonary vascular markings

Astley and co-workers<sup>1</sup> proposed a classification of tricuspid atresia based solely on the x-ray appearance of pulmonary vascular markings. Two groups were identified: (A) Decreased pulmonary vascular markings and (B) Normal or increased pulmonary vascular markings. A similar classification based on the pulmonary blood flow was used by Grisul and collaborators<sup>15</sup> but they further divided each group on the basis of associated cardiac defects. Often there is progressive diminution in pulmonary blood flow with increasing age.<sup>1</sup> Dick and associates<sup>16</sup> added a third group to Astley's classification: Group C—transition from increased to decreased pulmonary vascular markings in serial x-rays. This classification is listed in Table II. Although the principles of this classification are sound and the classification has some clinical value, it bypasses the anatomic groups (to be discussed). With the need for obtaining precise physiologic and anatomic details from cardiac catheterization and angiography prior to surgical intervention, classification by radiographic pulmonary vascular markings is inadequate for clinical use.

### III Classification based on associated anatomic defects

A classification based on the interrelationship of the great arteries was first proposed by Kuhne in 1906<sup>4</sup> and was later expanded by Edwards and Burchell. This classification was refined and popularized by Keith and associates.<sup>2</sup> This or a slight modification of it is the most commonly used classification.<sup>2,24</sup> A classification derived from several of these sources is presented in Table III. The designation of Types I and II was based on the interrelationship of the great arteries.

Type I Normally related great arteries  
Type II D transposition of the great arteries  
Type III L transposition of the great arteries

Further subdivision of Type I and II is largely dependent upon the status of the pulmonary arteries.<sup>25</sup> (a) pulmonary arteries present, (b) pulmonary hypoplasia and (c) no pulmonary hypoplasia. In Type I cases (normally related great arteries) the ventricular septal defect is absent (intact ventricular septum) in subgroup a or small in subgroup b or large in subgroup c. In Type II (D transposition of the great arteries) a large sized ventricular septal defect was always to be present in all subgroups.<sup>25</sup> In connection to the subgrouping of Types I and II, Type III (L transposition of the great arteries) was not subdivided on the basis of pulmonary arteries.<sup>25</sup> These subgroups were (a) pulmonary or subpulmonary stenosis and (b) aortic stenosis.<sup>25</sup> The inconsistency in subgrouping of the three types is apparent. Furthermore conotruncal anomalies other than D and L-transposition such as double outlet right or left ventricle and truncus arteriosus can occur with tricuspid atresia.

Keith and associates' classification does not take the great vessel anomalies other than D or L transposition into account, albeit they are few in number.

Tandon and Edwards<sup>26</sup> analyzed 45 pathologic specimens and classified tricuspid atresia based on positional abnormalities of the great arteries (Table IV). Apart from the criticism of this paper offered by Anderson and associates,<sup>27</sup> one might note that they included both L transposition (ventricular inversion) and L malposition (L relationship of great arteries without ventricular inversion or isolated bulbar inversion) into a

Table IV Classification of tricuspid atresia by Tandon and Edwards

I	Normally related great vessels
Subgroup a	Pulmonary atresia
Subgroup b	Pulmonary or subpulmonary stenosis
Subgroup c	No pulmonary stenosis
II	Inverted position of the great vessels
Subgroup a	Inverted great vessel
Subgroup b	Pulmonary or subpulmonary stenosis
Subgroup c	No pulmonary stenosis
III	Inverted great vessels
Subgroup a	Pulmonary atresia
Subgroup b	Pulmonary or subpulmonary stenosis
Subgroup c	No pulmonary stenosis
IV	Double outlet
Subgroup a	Pulmonary atresia
Subgroup b	Pulmonary or subpulmonary stenosis
Subgroup c	No pulmonary stenosis
V	Pericardial truncus arteriosus

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Table V Classification of tricuspid atresia based on ventriculoarterial connections by Anderson et al

I	Normal relations
II	L malposition
III	D transposition
IV	L transposition
V	Double-outlet chamber
VI	Pericardial truncus arteriosus

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subgroup of their Type II and named them L transposition. Additionally, this classification is complex and difficult to follow and presumably this is the reason for its not being included in recent textbooks of Pediatric Cardiology.<sup>2,24</sup> The great vessel anomalies were classified in an entirely different manner by Anderson and colleagues<sup>27</sup> (Table V). Therefore it is important that we have a unified classification so as to include all variations in the anatomy of the great vessels and to maintain uniformity of subgrouping. Accordingly the following classification is proposed. The primary grouping continues to be based on positional abnormalities of the great arteries as follows:

Type I Normally related great arteries  
Type II D transposition of the great arteries

Table VI A new classification of tricuspid atresia

Type I Normally related great arteries	Each Type and Subtype are divided into Subgroup a Pulmonary atresia Subgroup b Pulmonary stenosis or hypoplasia Subgroup c Normal pulmonary arteries (no pulmonary stenosis)
Type II II trans position of the great arteries	
Type III Malpositions of the great arteries other than D transposition	
Subtype 1 L trans position of the great arteries	
Subtype 2 Double outlet right ventricle	
Subtype 3 Double outlet left ventricle	
Subtype 4 D malposition of the great arteries (anatomically corrected malposition)	
Subtype 5 L malposition of the great arteries (anatomically corrected malposition)	
Type IV Persistent truncus arteriosus	

Type III Malpositions of the great arteries other than D transpositions

Type IV Persistent truncus arteriosus

Note that each type is identified with a Roman number. The Type I and II are the same as in the original classification put forward by Kuhne by Edwards and Burchell and by Keith and associates. Type III is different from that proposed by Keith and associates in that all malpositions of the great arteries with the exception of D transposition are included instead of only L transposition. The reason for the inclusion of all malposition with the exception of D transposition is because of the rarity of these abnormalities in association with tricuspid atresia. However there are many types of great vessel abnormalities and these can be further divided into subtypes.

Subtype 1 L transposition

Subtype 2 Double outlet right ventricle

Subtype 3 Double outlet left ventricle

Subtype 4 D malposition (anatomically corrected malposition)

Subtype 5 L malposition (anatomically corrected malposition)

Only the great vessel anomalies that have thus far been reported in association with tricuspid atresia have been included. As more positional anomalies of the great arteries (e.g. A transposition and A malposition) in association with tricuspid atresia are reported new subtypes to Type III may be added. Note that each subtype is indicated by an Arabic number. Type IV is reserved for cases of tricuspid atresia with truncus arteriosus. The major types (I to IV) including the subtypes of Type III may be subdivided into

Subgroup a Pulmonary atresia

Subgroup b Pulmonary stenosis or hypoplasia

Subgroup c Normal pulmonary arteries (no pulmonary hypoplasia)

Note that each subgroup is indicated by a lower case letter

The inclusion of the status of the interventricular septum i.e. intact septum small or large ventricular septal defect within each subgroup has been attempted by others<sup>11,12</sup> (Table III). However it may be advisable not to consider the status of the interventricular septum for the purpose of classification into subgroup a, b and c. A case we previously reported<sup>13</sup> was of Type I with pulmonary atresia but had a good size ventricular septal defect. Because it did not fit into any of the then existing classifications (subgroups) we proposed a new subgroup d. It is probably more appropriate to retract that suggestion and approach the problem in a different manner. After classifying tricuspid atresia into major Types I, II, III or IV (and into subtypes if it was type III) on the basis of great artery relationship and then into subgroups a, b or c on the basis of pulmonary arteries (atretic, stenotic or normal) one may then simply state the status of the ventricular septum—i.e. intact, small or large ventricular septal defect or multiple ventricular septal defects for any given case. Thus the above referenced case would be described as Type Ia with large ventricular septal defect. The a, b or c subgrouping could be carried through each major type (or subtype). The status of the interatrial septum and other associated malformations like aortic or subaortic stenosis, patent ductus arteriosus, persistent left superior vena cava, coarctation of aorta or anomalous pulmonary venous return if present could then be

stated for each case. A unified classification based on these principles is presented in Table VI. This classification is simple and maintains uniformity in subgrouping but at the same time takes into account all variations in great artery anatomy that have been described in association with tricuspid atresia. Should new anomalies come to light in the future, this classification may easily be expanded. It also preserves the basic principles of classification outlined by Kuhne<sup>6</sup> by Edwards and Burchell<sup>7</sup> and by Keith, Rowe and Vlad<sup>8</sup>, so that this can easily be adopted by cardiologists, surgeons and pathologists. This classification also follows the terminology of congenital heart disease proposed and reemphasized by Van Praagh<sup>1</sup> with regard to the conotruncal anatomy. One could easily include the remaining segmental subsets, namely viscerotransposed situs and ventricular loop and describe each case by the notations [(S D S) (S D D) (S D L) and so on] as the case may be.<sup>10</sup>

In summary, tricuspid atresia has been classified on the basis of morphology of the atretic tricuspid valve, x-ray appearance of pulmonary vascular markings and associated cardiac defects. The limited clinical usefulness of the first two types of classifications has been pointed out and it is suggested that anatomic classifications based on the associated defects is more useful. Recent advances in corrective surgery demand that we know the exact anatomy. Additionally, this information necessary for classifications is usually available after catheterization and angiography studies prior to palliative or corrective surgery. It is recommended that anatomic classification based on the associated defects as proposed here (Table VI) be adopted for general use.

Bruce S. Alpert, M.D., Wesley Covitz, M.D., Martin J. Frank, M.D., William B. Strong, M.D., and Paul M. Weinberg, M.D., provided critical review of the manuscript.

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## Calcium antagonists

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Calcium antagonists represent a new class of drugs of considerable theoretical and practical importance. Most of the drugs grouped together under such name are not available on the market in North America but many clinical trials suggest that they are valuable in the treatment of various cardiovascular abnormalities.

Calcium antagonists as implied by the name interfere with the normal function of  $\text{Ca}^{2+}$  in the body including that in the excitation-contraction coupling in smooth muscle and in cardiac muscle. Their effect according to Fleckenstein<sup>1</sup> is explained by a selective blockade of the slow channel of the cell membrane—i.e. by interference with the transmembrane  $\text{Ca}^{2+}$  influx. Our own research suggests that other sites of action are also important.

Calcium ions are recognized as playing an important role in the contractile process of the heart, smooth muscle and skeletal muscle in glandular secretion and in the release of neurotransmitters. In view of this it is rather surprising that calcium antagonists can be used therapeutically having apparently a rather selective action on the cardiovascular system without important side effects.

### Diagrammatic presentation

Fig. 1 lists the drugs grouped together as calcium antagonists by Fleckenstein. Besides these agents of variable chemical structure several other drugs are known to interfere with the availability of  $\text{Ca}^{2+}$  for contraction of smooth muscle. The relaxant effect of diazoxide, nitro-

glycerin, papaverine and hydralazine depend to a great extent on the extracellular calcium concentration and their action just like that of drugs listed in Fig. 1 is diminished in the presence of extra  $\text{Ca}^{2+}$  in the tissue bath. Sodium nitroprusside, another direct acting vasodilator was found to result in a dose related increase of calcium efflux from vascular strips.<sup>2</sup> There is an important difference however between the pharmacological action of other smooth muscle relaxants and calcium antagonists namely that depression of cardiac contractility is characteristic only for the latter drugs.<sup>1,3</sup>

### Mechanism of action

The basic mechanism of action of calcium antagonists more precisely the exact site of their action is not yet clarified. In isolated cardiac muscle depression of contractility could be demonstrated without any alteration in the upstroke velocity of the action potential only with slight abbreviation of the plateau phase. From these experiments and others demonstrating an effect on the action potential after  $\text{Na}^{+}$  flux was inhibited, Fleckenstein concluded that calcium antagonists act by selective inhibition of the calcium influx through the cell membrane. If this mechanism would be the only explanation for their action calcium antagonists should inhibit  $^{45}\text{Ca}$  uptake by the cells when measured with the lanthanum methods.<sup>4</sup> However in our experiments exposure of electrically driven rat atrium to verapamil, nifedipine or diltiazem in concentrations which depress cardiac contractions did not cause any diminution in uptake of lanthanum resistant  $\text{Ca}^{2+}$ . Similarly calcium antagonists failed to reduce uptake of lanthanum resistant calcium in rabbit mesenteric vein of rat aorta. This was so even in vessels in which calcium influx was enhanced by exposure to 60 mM  $\text{K}^{+}$ .

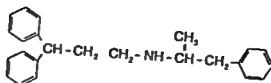
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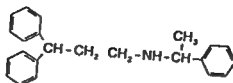
Reprint requests: Dr. T. T. Zsotér, Dept. of Pharmacology, University of Toronto, Toronto, Ontario, M5S 1A8, Canada.



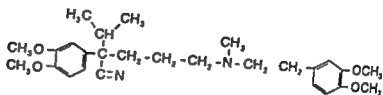
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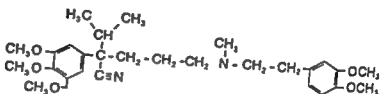
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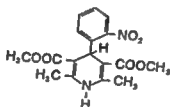
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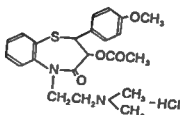
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Methoxyverapamil



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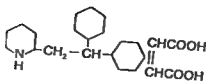


Fig Calcium antagonistic drugs and their structures

On the basis of these and other experiments on 'Ca efflux' as well as reports of other authors<sup>7,8</sup> we conclude that calcium antagonists must act on other sites as well as the cell membrane. We postulate that these agents interfere with the availability of Ca<sup>2+</sup> for contraction of vascular smooth muscle and cardiac muscle mainly intracellularly by inhibiting the release of Ca<sup>2+</sup> from various pools.

### Pharmacology

The effect of calcium antagonists on the smooth muscle in vessels and other tissues is similar to that of the direct acting vasodilators such as hydralazine, diazoxide, nitrites, etc. The relaxation of smooth muscle and the prevention of norepinephrine, angiotensin, methacholine, K<sup>+</sup> or barium chloride induced contractions is not mediated through any specific action on alpha or beta adrenergic or cholinergic receptors.<sup>9,10</sup> Calcium antagonists increase blood flow not only in coronary but also in mesenteric, renal and femoral vessels.<sup>11,12</sup> Many studies indicate blood pressure lowering in animals as well as in man.<sup>13,14</sup> Various calcium antagonists consistently were found to decrease systemic vascular resistance.<sup>15</sup> In addition, pulmonary arterial pressure was reported to be lowered.<sup>16</sup>

The cardiac effect of calcium antagonists *in vitro* is different from that *in vivo*. In isolated papillary muscle or in other *in vitro* preparations they cause a dose-related depression of cardiac contractions and dp/dt.<sup>17</sup> In this respect the effect was nifedipine greater than verapamil which in turn was greater than diltiazem.<sup>18</sup> *In vivo* however, the decrease in blood pressure activates baroreceptor reflexes with consequent increase in contractility (as measured by max dp/dt, ejection fraction) or decreased left ventricular end-diastolic pressure and heart rate resulting in higher cardiac output when calcium antagonists are given in therapeutic doses.<sup>19</sup> Consequently, *in vivo* one can not expect the higher coronary blood flow to be associated with lower myocardial oxygen uptake as found in isolated heart preparations.<sup>20</sup> Calcium antagonists were reported to protect the myocardium from ischemia induced changes by enhancing coronary blood flow and also by other mechanisms.<sup>21</sup> Further more reduction of infarct size after coronary ligation and enhanced development of collateral circulation was claimed by some studies.

Table 1 Clinical indications

Angina pectoris
Variant angina
Arrhythmia
Hypertension
Hypertensive crisis
Hypertrophic cardiomyopathy
* Chronic refractory heart failure

Antiarrhythmic properties of verapamil and diltiazem were demonstrated against arrhythmias induced by various methods such as ouabain, chloroform-epinephrine and coronary ligation.<sup>22,23</sup> Slowing the AV conduction and increasing the refractory period of the AV node were suggested as the principal mechanism for the antiarrhythmic effect.

Diltiazem was found to increase sodium diuresis to a greater extent than was explained by its effect on enhancing renal blood flow.<sup>24</sup> Such an action if confirmed could mean an important advantage over other drugs used in treatment of angina pectoris or hypertension. At present there is little or no evidence that calcium antagonists would have any other significant pharmacological effect than those mentioned above.

Studies on pharmacokinetics of verapamil indicate an almost complete oral absorption and a rapid biotransformation of the drug.<sup>25,26</sup> First pass metabolism in the liver must be quite significant as the bioavailability of oral doses is reduced to 10 to 22%. Information on pharmacokinetics of other calcium antagonists is far from being adequate.

### Therapeutic use

Table I lists clinical situations where calcium antagonists may be of value.

Most of the clinical studies were concerned with the use of calcium antagonists in angina pectoris. The fact that these drugs increase coronary blood flow, decrease arterial pressure and have an antiarrhythmic effect would suggest their value as antianginal agents. Furthermore, in contrast to propranolol, these drugs could also be used in patients with bronchospasm. In addition to uncontrolled clinical trials, there were some double blind studies which indicated these drugs superior to placebo in reducing the number of daily attacks, necessitating less nitroglycerin consumption and in improvement of exercise

tolerance<sup>31,3</sup> These effects were reported when verapamil was given in doses of 80 mg three times a day or more<sup>31,32</sup> nifedipine 10 mg four times a day<sup>31</sup> and perhexiline 200 mg twice a day<sup>31</sup> Others using the same or lower doses of verapamil or nifedipine failed to observe significant improvement over placebo treatment None of the studies has proven superiority of calcium antagonists over propranolol in the prevention of anginal attacks<sup>31,3</sup>

The most convincing results with calcium antagonists were obtained in variant angina Several authors reported that patients treated with verapamil nifedipine or diltiazem became symptom free or markedly improved and attacks associated with ST elevation in the electrocardiogram occur much less frequently<sup>33,34</sup> The largest series was that of Hosada and Kumura<sup>33</sup> who found that 30 of 47 patients with variant angina became symptom free while on nifedipine<sup>33</sup> Thus calcium antagonists seem clearly superior to propranolol in the treatment of Prinzmetal's variant angina but not of effort angina The effectiveness of calcium antagonists in variant angina can be explained by the ability to prevent coronary vasospasm

Clinical experience in the treatment of arrhythmia is confined mainly to verapamil given intravenously This drug was shown in several studies to be effective in causing the termination of paroxysmal supraventricular tachycardia when given intravenously and in preventing the recurrence of attacks when given orally<sup>37,38</sup> In ventricular arrhythmias however verapamil was less effective As to atrial fibrillation in one study intravenous verapamil reduced the ventricular rate in 111 of 115 patients but converted the fibrillation to sinus rhythm in only one patient<sup>39</sup> More experience is required before we may conclude about the effectiveness of various calcium antagonistic drugs in the treatment of arrhythmias

Hemodynamic evaluation both in animal and human experiments consistently demonstrated that calcium antagonists cause a dose related decrease of systolic and diastolic pressure In view of these results the scarcity of controlled clinical trials to investigate the value of these agents in the treatment of hypertension is rather surprising This is particularly true when considering that in vessels of spontaneously hypertensive rats

abnormal  $\text{Ca}^{2+}$  handling was demonstrated suggesting the possibility that calcium antagonists might offer a more logical treatment of hypertension than other vasodilators<sup>40,41</sup> Guazzi and colleagues<sup>42</sup> reported a pronounced decline of arterial pressure after oral or sublingual nifedipine in patients with severe hypertension including three with hypertensive encephalopathy<sup>42</sup> The prompt onset of action described by these and by other authors<sup>43</sup> suggests that this drug might be of great value in the treatment of hypertension emergencies Aoki and others observed a significant lowering of systolic and diastolic pressure of long duration in hypertensive patients a single dose of 30 mg nifedipine remained effective during a 10 hour long observation period

Hypertrophic cardiomyopathy may be another indication for the use of calcium antagonists as verapamil was reported to improve exercise capacity in these patients<sup>44</sup> There is no evidence however that these drugs would be useful in the treatment of refractory heart failure As nifedipine has no venodilator effect<sup>45</sup> and there is no indication that other calcium antagonists would have either they are unlikely to be as effective as nitrites or sodium nitroprusside in reducing cardiac preload

### Side effects

Side effects mostly headache and dizziness were reported in 9% of 8 072 patients treated with verapamil<sup>39</sup> Side effects with nifedipine were encountered in 17% of 5 008 patients but they were usually only minor occurrences such as headache heat sensation vomiting or nausea<sup>46</sup> Perhexiline was found to cause side effects quite frequently<sup>3</sup>

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## Exercise testing for the diagnosis of coronary artery disease

The exercise test has been the standard noninvasive test to help confirm or exclude the diagnosis of coronary artery disease. The time honored criterion for myocardial ischemia is ST segment depression which although being an electrophysiological abnormality has been most often correlated with findings at coronary arteriography which then confirm an anatomic abnormality. Recognizing the limitations of coronary arteriography itself to diagnose coronary disease and the fact that myocardial ischemia may be present without the presence of coronary disease (such as in patients with valvular heart disease or hypertension) most previous studies have demonstrated that the presence of an abnormal ST segment response to stress almost always correctly predicted the presence of coronary artery disease. However these studies largely consisted of males referred to the catheterization laboratory for chest pain complaints who would be expected to have a high pre test (exercise) risk of coronary disease. Recently some reports have demonstrated that when patients with a low pre test risk such as asymptomatic men or women with atypical chest pain have been subjected to exercise testing and subsequent coronary arteriography a disturbingly high rate of false positive exercise tests has resulted although most reported series dealt with small numbers of patients. In order to evaluate how much additional information analysis of the ST segment response to exercise could yield for the prediction of coronary disease beyond that which was available from a detailed description of chest pain and the sex of a patient in a large cohort of patients we recently correlated certain clinical and exercise data with coronary arteriography from the National Collaborative Study on Coronary Artery Surgery (CASS).

The patient population was derived from 15 participating centers broadly distributed throughout the United States and Canada and consisted of 1460 men and 580 women. All patients underwent graded exercise testing using the Bruce protocol and cardiac catheterization. The exercise test was

considered positive when there was  $\geq 1$  mm. of ST segment depression or elevation. Significant coronary artery disease was defined as  $\geq 70\%$  narrowing of the diameter of at least one major coronary vessel. The chest pain complaints of the patients were categorized into three groups: definite angina, probable angina, and nonischemic chest pain. Patients having prior myocardial infarction or taking digitalis at the time of the exercise test were excluded from the analysis.

The results of the study are summarized in Table I. The pre-test risk of coronary disease varied from 5% to 89% depending upon the sex of the patient and the description of chest pain. A positive exercise test only increased the pre-test risk by 1% to 14% whereas a negative test lowered the risk by only 0% to 29%. When the pre test risk of coronary disease was high (e.g., men with definite angina) a positive exercise test was highly correlated with the presence of coronary disease although it only slightly increased an already high pre-test likelihood of coronary disease; however a negative exercise test in this subgroup was more likely to be falsely negative. Conversely when the pre test risk of coronary disease was low (e.g., women with nonischemic pain) a negative exercise test was highly predictive of the absence of coronary disease although again only confirming an already low pre-test likelihood of coronary disease, whereas a positive exercise test in this subgroup was more likely to be falsely positive.

The conclusion of this study indicates that before the results of exercise testing can be objectively evaluated the pre test risk of coronary disease must first be considered. Although the results from this study are derived from symptomatic patients the conclusion appears to support other studies showing that the percentage of false positive exercise tests among asymptomatic patients may be as high as 65%. A major limitation of the study is that only the ST segment was evaluated and there may be other exercise test variables which may prove more useful for the prediction and extent of coronary disease such as the heart rate and blood pressure.

**Table I** Pre test risk of coronary disease and predictive value of a positive and negative exercise test in the coronary artery surgery study (CASS)

History	Sex	No.	Pre test risk of coronary disease (%)	Predictive value (%)	
				+ ET*	- ET*
Definite angina	Male	670	89	96	35
Definite angina	Female	98	62	73	67
Probable angina	Male	594	0	87	56
Probable angina	Female	240	40	54	78
Nonischemic pain	Male	201	22	39	86
Nonischemic pain	Female	249	5	6	90

Predictive value of a positive exercise test (+ ET) = percentage of positive results that are truly positive.  
Predictive value of a negative exercise test (- ET) = percentage of negative results that are truly negative.

response to exercise and the amount configuration onset and duration of ST segment depression. Our study should not be used to minimize the importance of exercise testing in evaluating arrhythmia, confounding symptoms, responses to therapy (medical and surgical) and work capacity. However, when used for the diagnosis of coronary disease in the positive-negative classification it appears that the results of exercise testing are limited in improving upon an estimate of the probability of coronary disease based upon the classification of chest pain and the sex of the patient.

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## The risk of coronary angiography and National Health planning

Ever since the development of selective coronary angiography, physicians have been concerned about the risks of this valuable diagnostic test. After the success by Sones and Shurey with low complication rates, others were initially frustrated in their attempts to duplicate their results. The percutaneous femoral technique and Judkins' precurved catheters made the procedure easier but may have encouraged those less prepared to try coronary angiography and complications were frequent. During the sixties as many of the major medical centers were learning the procedure frequently by self education, relatively few studies were done. The success of coronary bypass surgery at the end of the decade led to an explosion in the number of hospital done coronary angiographies. Since there were few trained coronary angiographers, complication rates in these medium-sized hospitals were high. As physicians in these laboratories learned the painful lessons previously learned in the larger institutions.

Many efforts have been made to develop the proper indications for safety of coronary angiography. It is understandable that an experienced angiographer team is required to

level of experience to prevent unnecessary complications has been difficult to define since the patient population is inherently at some risk regardless of the laboratory conditions. It is, perhaps, natural for those associated with major medical centers to assume that large case loads are necessary and the surveys of Adams and Abrams have often been interpreted to indicate an inverse relationship between case loads and complication rates. However, these surveys were done during the early seventies and probably reflect the lack of experienced angiographers in the moderate-sized laboratories. This can be surmised from the dramatic improvement in complication rates between the first and second surveys in the smallest laboratories using the femoral technique. Recent surveys in our state have shown that well trained angiographers can start new laboratories and have remarkably low complication rates even when performing fewer than 150 cardiac catheterizations per laboratory per year.

The Washington State experience has major implications for health planning. The present National Guidelines for Health Planning tend to favor the concept of a few major

heart centers with dedicated cardiac catheterization laboratories and accompanying cardiac surgery programs. These centers will always be important, but we should not discourage the development of regional dual purpose diagnostic laboratories. There is a need for angiographic equipment in hospitals located in large population areas surrounding major cities or distant from major cities for emergency angiographic studies. If these laboratories can also be utilized for coronary angiography as they are in the State of Washington, the utilization of this expensive equipment is significantly improved and there is better patient access to this valuable diagnostic test.

The existing National Guidelines for Health Planning were established in spite of the absence of studies to indicate that these guidelines would improve on either the safety or the cost of cardiac catheterization or cardiac surgery. These cardiac catheterization guidelines are inappropriate because they represent an attempt to set numerical standards based on outdated opinions and data. Medicine has always been a dynamic profession and it is time to accept the fact that the optimal conditions for coronary angiography and cardiac surgery have changed. If health planners must have guidelines let us at least base such guidelines on objective data and leave them flexible enough to adapt to changing circumstances and local health care needs.

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## Bladder trauma from jogging

The current popularity of jogging is bound to throw up its share of traumatic complications like any other sporting activity. One of these has been hematuria, either microscopic or macroscopic. While strenuous exertion may give rise to rhabdomyolysis and myoglobinuria, the more restrained exercise of jogging may be less likely to produce these symptoms. Neither is there the likelihood of the generalized splanchic vasoconstriction of extreme exertion and the resultant ischemic renal injury.

On the other hand the rhythmic relaxed style of the jogger favors the circumstances which can provoke the bladder lesion I have observed in a number of long distance runners. I have only found these in men and the hematuria which was profuse in some occurred on the first occasion of urination following the running event. The discoloration of the urine usually disappeared within 24 hours. Sometimes

small clots were passed and there was dull suprapubic pain with dysuria. The episode was either an isolated or an occasional event.

Cystoscopy within the first few days of the symptom shows well-defined localized contusions on the posterior rim of the internal meatus, the inter-ureteric bar and its extensions over the intramural ureter and a mirror image of these lesions on the posterior bladder wall, the most dramatic of which is a midline lesion in which a rim of contused tissue encircles a small island of normal urothelium. These appearances resolve rapidly so that cystoscopy a week or more afterwards is likely to be entirely normal.

The consistency of location of the contusions suggests they are produced by the impact of the flaccid posterior bladder wall against the projections of the inter-ureteric bar and internal meatus which in the male are thrown into



prominence by the underlying mass of the prostate. The prostate additionally transmits the counter impact of the rhythmic contraction of pelvic floor muscles in accompaniment of each step of the run. At the instant of coming down on the foot the descent of the abdominal viscera forces the flaccid posterior wall of a nearly empty bladder into contact with its floor. Although each impact itself is probably minor repetition during the course of a long run or jog produces trauma. The bladder content is probably critical, since when it is completely empty both walls will be in apposition with no oscillation and therefore no impact of the surfaces whereas filling beyond a certain volume will ensure that the posterior bladder wall never contacts the trigone at any stage. This critical volume is the likely explanation for the phenomenon being only an occasional or solitary event in someone who jogs regularly. Bassler<sup>2</sup> has already drawn attention to prophyllaxis in the form of a liter of beer before running or jogging<sup>1</sup>.

The lesions in themselves are unimportant but knowledge of their occurrence provides the simple explanation for an

alarming symptom. The degree of exertion in jogging is unlikely otherwise to traumatize a normal urinary tract but may provoke bleeding from a renal or bladder tumor, a renal cyst or hydronephrosis. The possibility of these occurrences necessitates upper and lower urinary tract investigation in all cases of hematuria following exercise.

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## Of pulmonary venous receptors

As indicated previously, the heart is one organ made of two pumps (the right and left ventricles). These two pumps must be exquisitely synchronized to avoid serious circulatory disturbances, such as congestive heart failure (CHF), acute pulmonary edema and other circulatory problems. The regulation of these two pumps must depend upon the central and autonomic nervous systems and associated extremely sensitive receptors in the pulmonary veins, atria and superior and inferior venae cavae. Some of the reflexes are already known—i.e. the Bainbridge reflex—but the receptors and reflexes in the pulmonary venous system are unknown or little known. On the basis of physiologic logic and medical clinical theory there must be pulmonary venous receptors and reflexes which are major regulators of the synchronization of performance of the two pumps which constitute the heart. The chemodectomas, closely associated with the pulmonary veins and so common and widespread in the small pulmonary veins of patients with CHF, surely represent hypertrophy from work of cardiac regulator receptors. These regulators of the

stroke volume and output of the right ventricle and left ventricle indicate the existence of normal pulmonary venous receptors and regulating reflexes yet to be anatomically and physiologically identified and defined.

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## On Duroziez's disease

### To the Editor

Ward concludes that the different patterns of acute and chronic valvular involvement being dependent on whether or not the patient had rheumatic fever suggest more than one etiologic agent may be responsible for what is currently regarded as a single entity—rheumatic heart disease. The argument is as follows:

**The happenings** 7 Of 248 children treated for acute rheumatic fever<sup>1</sup> Ward found that those with isolated carditis had a higher incidence of mitral systolic and mitral diastolic murmurs and cardiomegaly than those with arthralgia, polyarthritis, and chorea. Moreover the incidence of pericarditis was higher in those with isolated carditis, even when compared to the group with polyarthritis and comparable severe carditis. On the other hand, those with isolated carditis had a lower incidence of subcutaneous nodules and aortic regurgitation than those with arthralgia and polyarthritis with comparable severe carditis.

Of 296 patients with chronic valvular heart disease 164 had a history of rheumatic fever and 132 did not. The former had a significantly higher incidence of mitral stenosis and regurgitation and aortic disease. On the other hand, isolated mitral stenosis was much more common in those free of a history of acute rheumatic fever.

The notion Ward reasoned that "If all cases of acute valvulitis have a common etiology, they should have either similar clinical features or fit into a definable clinical syndrome and in chronic valvular heart disease the pattern of valvular involvement should not be affected by the presence or absence of a rheumatic history. Ward concludes therefore that isolated mitral stenosis is not commonly a sequela of acute rheumatic fever."

**The name** Therefore Ward concludes that the label "rheumatic valvular heart disease" should be restricted to incidences with a history of acute rheumatic fever and that isolated mitral stenosis without a past history of acute rheumatic fever does not merit the name "rheumatic heart disease." If a name for isolated mitral stenosis of unknown cause is wanted, I suggest resurrecting Duroziez's disease<sup>2</sup> after the clinician who on the basis of his clinical observations, came to the conclusion that at least half of all subjects with isolated mitral stenosis did not have rheumatic heart disease. Vaquer<sup>3</sup> devotes an entire chapter on this disorder in his classic book on diseases of the heart.

**Comment** The history of medicine is replete with examples that prove that Ward's notions are not always correct. Markedly dissimilar clinical disorders may be due to a common etiology (e.g. meningococcemia and meningococcal meningitis) and similar clinical syndromes may be due to diverse etiologies (e.g. pernicious anemia "Bright's disease"). Manifestations of a clinical disorder (disease) depend upon the reaction of an individual to his total environment including the essential (etiologic) agent.

Nevertheless, Ward I think, is correct when he demands evidence for the inference that isolated mitral stenosis is necessarily always of rheumatic origin. One cannot use architectural evidence because there are infinite deleterious agents and only a finite number of ways that tissues can respond to injury. Furthermore, mitral valve surgery for isolated mitral stenosis and death due to this disorder occur so long after the

development of the lesion that immunological abnormalities and inflammatory changes that may have been present soon after the onset of the acute illness are no longer present. One must therefore turn to observations of clinicians who have followed subjects closely both before and after the onset of clinically recognized isolated mitral stenosis.

Walsh, Bland and Jones have done this. They report on 48 patients who have been observed before and after the stage of pure mitral stenosis and in 33 only after the signs of pure mitral stenosis were already established. Of the 48 27 initially had signs of mitral regurgitation with or without signs of other lesions. The other 21 had no detectable valvular disease after recovery from their acute illness. Of these two developed mitral regurgitation, three developed mitral regurgitation and stenosis but later developed signs of pure isolated mitral stenosis. But in 10 patients (21%) the valvular lesion began and remained as pure isolated mitral stenosis years after the acute illness. It is particularly to be noted that most of these patients were considered to have a mild form of rheumatic fever on the basis of the absence of a recognizable illness prior to the appearance of heart disease in four, a period of poor health of obscure nature immediately preceding the appearance of heart disease in three, and in addition 10 poor health, either characteristic joint pains or chorea in the remainder. The conclusion "In some of their younger patients who were under close observation at the time of their active disease it had been impossible to identify clearly as rheumatic fever their mild illness prior to the appearance of characteristic signs (of mitral stenosis) in the heart."

In her classic monograph, May Wilson wrote "Cardiac abnormalities in the absence of a history or evidence of rheumatic fever do not warrant a diagnosis of rheumatic heart disease." No one adheres to this dictum even when inflammatory and immunologic evidence is lacking.

The mitral valve would indeed be unique if only one cause were responsible for the development of mitral stenosis. Burch and Ward and others have already obtained evidence supporting other causes. From the pragmatic standpoint one must decide whether anything is gained or lost by the gratuitous addition of the label "rheumatic."

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# Incidence of thrombocytopenia in medical patients on mini dose heparin prophylaxis

To the Editor

Prophylactic low dose subcutaneously administered heparin has been increasingly advocated and utilized in high risk surgical and medical patients groups. However there have been a number of recent reports of thrombocytopenia occurring during the course of therapeutic heparin administration<sup>1</sup> some associated with serious sequelae. Thus in one prospective study it was reported that 31% of patients on continuous heparin infusion had significant thrombocytopenia and routine platelet counts have been advocated to identify this problem when it occurs. Anecdotal accounts of thrombocytopenia in patients on low dose subcutaneous heparin utilized prophylactically have also recently been reported raising the question of how prevalent and clinically common the complication of thrombocytopenia is with low dose prophylactic heparin. To date and to the best of our knowledge the complications of subcutaneous prophylactic heparin have only been analyzed carefully in surgical patients. In an attempt to further investigate this problem we performed a prospective study of patients on low dose subcutaneous prophylactic heparin in a medical service to determine the frequency of thrombocytopenia.

From November 1978 to April 1979 50 male patients received subcutaneous prophylactic heparin for at least 5 days while on the medical service at the Salt Lake City Veterans Administration Medical Center. The decision to treat was based on clinical indications in each patient made entirely by the ward house staff caring for the patient. Baseline platelet counts were obtained prior to heparin administration and then on a daily basis excluding weekends. Informed consent was obtained. Platelet counts were done in triplicate by the Coulter counter method and the average of three counts was used. Significant thrombocytopenia was defined as a 30% decrease in platelet count from our baseline values. The daily heparin dose prescribed was left to the discretion of the ward staff with 26 patients (52%) receiving 5 000 USP units every eight hours and 24 patients (48%) receiving 5 000 USP units every 12 hours. The patients' diagnoses were noted as were the indications for treatment.

Results showed that in the 50 male patients only three (6%) had a significant fall in platelet count. One of these patients was receiving radiation therapy for a lung tumor during which platelet counts fell gradually consistent with radiation toxicity. In another patient septic shock was the probable cause of thrombocytopenia. In the third patient no obvious alternative explanation could be incriminated. Thus the incidence of thrombocytopenia in our study is probably 2%. This contrasts with the 31% incidence reported by Bell and associates in patients receiving heparin in therapeutic dosage.

Our results suggest that thrombocytopenia secondary to subcutaneous low dose heparin is an unusual complication in male medical patients. Thus we disagree with some authors who suggested daily or frequent platelet counts be obtained on all patients on heparin—at least for male patients such as occur at Veterans Administration Medical Centers who receive low dose heparin. Obviously such surveillance would be quite expensive considering the increasing utilization of subcutaneous low dose heparin prophylaxis. We suggest the alternative that male patients on subcutaneous low dose heparin be watched carefully for clinical evidence of thrombo-

cytopenia (i.e. bleeding petechiae) and in the event these occur then platelet counts should be obtained. Because our study only included male patients it is not clear to what extent these data are valid for female patients.

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## Cost of continuous infusion vs intermittent IV heparin

To the Editor

In a recent study in *THIS JOURNAL* Wilson and Lampman concurred with Mant and associates that the incidence of major bleeding is not significantly different with continuous infusion or intermittent intravenous (IV) heparin. Although more study is needed to resolve this controversy if the safety and efficacy are virtually the same for both methods of administration of heparin then the cost of each method needs analysis.

In order to demonstrate the potential savings that can be gained with the use of intermittent IV heparin therapy two commonly recommended heparin regimens for pulmonary embolism or deep vein thrombosis were compared.

Cost analysis of two common heparin regimens is shown in Tables I and II.

Comparing the hospital cost of each ten day regimen at list price a savings of \$114.06 is realized. Patient charges of course would far exceed this amount.

When a hospital savings of approximately \$100 in one patient are applied on a national scale the potential savings are significant. Wessler estimated that 250 000 cases of

**Table I** Regimen one (intermittent therapy) Heparin 5 000 units intravenous bolus immediately followed by 5 000 units intravenous bolus every 4 hours for ten days<sup>1\*</sup>

	Hospital cost (24 hours)	Hospital cost (10 days)
Heparin 5 000 units qsh	\$1 14	\$41 40
Needles and syringes	0 72 (\$0 12/unit)	7 90
Heparin 5 000 units (immediate one time dose)		0 69
Small vein infusion set for intermittent administration (changed every two days)	0 43 (\$0 85 set cost)	4 25
Total course		\$53 54

**Table II** Regimen two (continuous infusion therapy) Heparin 5 000 units immediate intravenous bolus followed by Heparin 10 000 units in 5% dextrose in water 500 ml to run every 10 hours (1000 units/hour via infusion instrument<sup>1\*</sup>)

	Hospital cost (24 hours)	Hospital cost (10 days)
Heparin 1 000 units/hour	\$3 31	\$ 33 31
Heparin 5 000 units (immediate dose)		0 69
DW 5% 500 ml at 50 ml/hr	6 12	61 90
Needle and syringe	0 24	2 40
	(2 units/24 hrs)	
Standard administration set (changed every 2 days)	0 66	6 55
	(1.31 set cost)	
Final filter (0.5 micron)	0 99	9 85
	(1 47 filter cost)	
Small vein infusion set (changed every 2 days)	0 36	3 60
	(7 9 set cost)	
Infusion pump	5 00	50 00
Total Course		\$167 60

Cost of controlled infusion device will vary with type and brand of infusion instrument used and if special administration sets are required.

pulmonary embolism are hospitalized in the US annually Coon and colleagues reported that there are approximately 950 000 clinically recognized cases of deep vein thrombosis in the US each year. Assuming only half of these patients receive intermittent heparin therapy (vs continuous infusion) as described above there could be an approximate hospital savings of 20 million dollars. Patient and third party payer savings would obviously be even more significant.

Other factors that need to be considered in a discussion on hospital costs for heparin administration include nursing personnel time for site care, monitoring, and rate adjustments of intravenous solutions for continuous administration versus the personnel time required for intermittent site care and the time required for an intravenous bolus. Mant and colleagues and Rosenblum allude to the fact that use of intermittent administration is generally less complex than continuous infusion. Nurses of the intravenous therapy team at the University of Tennessee Hospital Memphis prefer the intravenous bolus route over the continuous infusion for ease of administration and because there is less potential for error.

Additionally laboratory tests under most situations would

also be similar for either intravenous continuous or intermittent administration. It also must be mentioned in a discussion of heparin costs that many patients receive less than a 10-day course of heparin therapy (minimum course 7 days).

If further investigations concur with the work of Mant and colleagues and Wilson and Lampman (intermittent intravenous administration of heparin is as safe and effective as continuous infusion) we believe because of the potential cost savings intermittent heparin therapy to be the preferred method of administration.

More study is needed to resolve the controversy over which method is preferred. However as with other drug therapies if safety and efficacy are quite similar then cost of over all therapy must be assessed.

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## Reply

### To the Editor

Doctors Self and Vanderbush have shown that equipment and labor inputs for the intermittent method of heparin administration may be quite a bit less than for the continuous method. This is an undeniably pertinent fact bearing on the choice of a preferred method.

Our study suggested that neither method had a clear advantage in reducing risk of serious hemorrhage. The small numbers of patients in this study limits the certainty with which this conclusion is justified. Nevertheless, until convincing evidence of less efficacy or greater risk is presented we would agree that it is quite reasonable to recommend the intermittent method on the basis of economic considerations.

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## Book reviews

**Exercise and Coronary Heart Disease** By Gerald F. Fletcher and John D. Cantwell, Springfield, Ill. 1979. Charles C. Thomas, Publisher. 340 pages. Price \$27.50.

This publication concerned with exercise and coronary heart disease consists of 14 chapters which review fairly completely the relationship of sedentary living and exercise to coronary heart disease. Among the subjects discussed are historical aspects, exercise physiology, exercise as a risk factor, lack of exercise as a risk factor, dangers of exercise and rehabilitation. A list of cardiac rehabilitation centers is included in Chapter 12. The present emphasis on exercise and rehabilitation makes this book timely. Readers will find the information interesting. This reviewer is of the opinion that physicians who treat the patients with coronary heart disease are best qualified to manage rehabilitation in each individual patient. They know them best. This book can assist doctors in outlining exercise training and advice. The book fails to provide convincing data as to whether or not exercise increases longevity. Readers certainly will learn from this book the trends in exercise advice given patients. The photograph of Paul White on page 5 is interesting.

**Management of Ventricular Tachycardia—Role of Mexiletine** Proceedings of a Symposium held in Copenhagen, May 25-27, 1978. Edited by E. Sandoe, D. G. Julian, and J. W. Bell. Copenhagen, 1978. 619 pages.

This is the proceedings of a symposium held in Copenhagen during May 1978 on a relatively new antiarrhythmic drug. The book is extensive. It includes many papers on ventricular tachyarrhythmias in particular. The pathophysiology of the arrhythmias, electrophysiology of the arrhythmias and drug action, choice of drugs, role of beta blockade and use of mexiletine are among the many subjects discussed. This is a very detailed review of the ventricular tachyarrhythmias, an extremely important problem in clinical practice. Those who study this publication will profit considerably from the time devoted. It is not an easy book to read or study. Nevertheless, it is a good book for all physicians, not only for cardiologists.

**Electrocardiographie Pratique—Second Edition** By R. Rulhière. Paris, 1978. Editions Masson. 532 pages.

This book in French is the second edition. It consists of a series of electrocardiograms recorded on patients with various clinical cardiac states. The clinical data on each patient which justified the recording of the tracing are briefly presented. A brief history and physical findings are presented. The electrocardiogram is interpreted and a brief comment is finally included to indicate the role of the ECG in the management of the patient's clinical state. The tracings are very good, the measurements are accurate, and the role of the tracing in the clinical study is discussed clearly. Those who are learning the use of the electrocardiogram in clinical practice will find this to be a good book. Nevertheless, to appreciate the tracings and their applications, it is best the reader should have a good background knowledge of the fundamentals of electrocardiography. The tracings are grouped into 14 different syndromes, such as that found in patients with dyspnea on effort, brief periods of chest discomfort, prolonged periods of discomfort, palpitation, syncope, hypertension, large hearts, cyanosis, and others. This is an interesting book and a good one for the study of clinical cardiology and electrocardiography by means of discussions of patients.

**Cardiology** By D. G. Julian. New York, 1978. Macmillan Publishing Company, Inc. 347 pages. Price \$13.00.

This paperback book is a good review in a few pages of the essentials of clinical cardiology. Those who have learned the physiology and pathology of the heart and circulation can profit most from this fine small book. It is in its third edition, an indication of its previous reception. The field of clinical cardiology is presented clearly and concisely for the benefit of the busy physician. This is a good book.

## Books received

**Manual of Emergency and Outpatient Techniques** Edited by Allen P. Klippel, MD, and Charles E. Anderson, MD. Boston, 1979. Little Brown & Company. 433 pages. Price \$10.95.

**Noninvasive Approaches to Cardiovascular Diagnosis** By Alfred F. Parisi and Donald E. Tow. New York, 1979. Appleton Century Crofts, Inc. 241 pages. Price \$12.95.

**Progress in Pharmacology** Vol. 2, No. 2. By H. Lüllmann, T. Peters, M. J. Mattila, and V. M. K. Venho. Stuttgart & New York, 1979. Gustav Fischer Verlag. 86 pages. Price \$26.00.

**Recovery of Resilience Overcoming Chemical Dependency** By George A. Mann, MD. New York, 1979. Harper & Row. 180 pages. Price \$8.95.

## Body Imaging Conference

The Fifth Annual International Body Imaging Conference will be held at the Kauai Surf Hotel, Kauai, Hawaii, October 11 through 14, 1980. The conference offers approximately 25 Category I AIA credits and will present to participants a correlated approach to the principles, indications, uses, interpretation and results obtained with computed tomography, ultrasonography and nuclear imaging. Course participation by practicing imaging physicians, residents, technologists and corporate personnel is encouraged. Fees for registration are \$350 (\$450) for physicians and \$225 for residents and technologists with letter registration is limited. Registration and inquiries should be addressed to: Conference Secretary, Fifth Annual International Body Imaging Conference, West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park, CA 91301.

## Symposium on Cardiac Arrhythmias and Conduction Defects

A symposium entitled "Electrophysiology of Cardiac Arrhythmias and Conduction Defects" will be presented at the Detroit Heart Hotel, Detroit, on September 25 through 27, 1980. The symposium is sponsored by the Michigan Heart Association and the Council on Clinical Cardiology of the American Heart Association. The Course Director is Seymour Gordon, MD. For further information contact: Michigan Heart Association, P.O. Box LV 160, Southfield, Mich. 48076. Telephone (313) 940-0000 for Eleanor D. Peterson, R.N.

## Health Sciences Communications Association

Health Sciences Communications Association will hold its 22nd Annual Convention in Calgary, Canada, on June 14 through 18, 1980. The convention theme is "Images for Health." For further information, contact: Stuart Wynn, Co-ordinator, Education Services, Faculty of Health Sciences, McMaster University, 1200 Main St. West, Hamilton, Ontario, Canada L8S 4J9.

## International Meeting on Cardioplegia and Myocardial Protection

This symposium will be held in London, England, on June 9 and 10, 1980, and will cover recent advances in the understanding of basic mechanisms of ischemic injury and the prevention or reduction of tissue damage during open heart surgery using the techniques of chemical cardioplegia and hypothermia. Methods of investigation of myocardial damage will be assessed, as will the rationale of formulation and use of cardioplegia solutions. In addition to an international list of speakers, participation is invited by delegates. For further information, please contact: Advisory Services Medical Symposia, 79 Wimpole Street, London W1M 7DD, England.

## IMPORTANT INFORMATION FOR AUTHORS

Effective June 1, 1980, all manuscripts for the AMERICAN HEART JOURNAL should be sent to:

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